

Discussion:

The Division stated that this proposal is satisfactory, and asked AZ to please use the same data format for clinical batch stability data as in the January 30, 2006, amendment. AZ asked if it is preferred that the individual data be tabulated as in the January 30, 2006, amendment and if they may retain the old stage groupings for this presentation of the [redacted] Compactor data. The Division stated that both of these proposals are acceptable.

Comment 4.i.(iv)

This comment pertains to your impurity method for formoterol fumarate dihydrate. Since the retention times are so close for peaks from [redacted] and the [redacted] impurity, modify the system suitability test to show adequate separation of these two peaks.

Prior to modifying the system suitability test to show adequate separation of these 2 peaks, AstraZeneca needs to perform the robustness work requested in Comment 4.j.(ii). In the event that the separation is not robust, or that the resolution criterion for this separation is difficult to achieve in routine testing, AstraZeneca proposes to amend the method to refer to the specific batch drug substance acceptance testing for the level of [redacted]. This is in accordance with previous communication with the Agency (IND 63,394, End of Phase 2 meeting held 4 April 2002) where it was agreed that process related impurities may be controlled/transcribed from drug substance acceptance testing. Does the Agency concur with this proposal?

Discussion:

The Division stated that this is a review issue (i.e., the results of your work will need to be assessed), however, the approach suggested appears reasonable, as long as [redacted] is only a process impurity and not a degradant (as appears to be the case). Clarify why the acceptance criterion for [redacted] is higher for the drug product (NMT [redacted]) than for the drug substance (NMT [redacted]) since it is not a degradant. AZ stated that this was to allow for variability in the drug product method. AZ will look at the robustness of the method, and will reevaluate the acceptance criterion for the drug product.

Comment 4.i.(xi)

The following comments pertain to the system suitability tests of the method for [redacted] leachables. Modify the criteria for resolution so that it is defined according to USP. Include a capacity factor. Include a standard to demonstrate that the method is capable of quantifying a peak near the level of the LOQ.

The method for [redacted] leachables in drug product will be modified so that the criteria for resolution is defined according to USP, and to include a standard to demonstrate that the method is capable of quantifying a peak near the level of the LOQ. Please clarify why a capacity factor is required.

Discussion:

The Division stated that this is a general recommendation, and AZ should provide a reason if they feel that it is not needed. However, it is not clear how the analyst identifies a particular _____ in a mixture of standard peaks. AZ stated that they are working on this and will provide a response. They stated that they will probably institute a capacity factor in the system suitability test.

Comment 4.k

Provide summaries and individual batch release data for individual cascade impactor stages and components. Account for the failures observed in the batch release data, relative to the proposed mass balance specification.

AstraZeneca will provide the requested summaries and individual batch release data in graphical and tabulated formats. With regard to the request to account for failures relative to the proposed mass balance specification, please clarify this request. Does the Agency wish AstraZeneca to provide an explanation for these failures including an outline of any investigations performed, or does this request relate to omitting all results associated with impactor runs failing the proposed mass balance criterion from the summaries to be provided?

Discussion:

The Division stated that our intent was to have an explanation for the failures. AZ stated that mass balance failures may be hard to explain, but they will do their best to speculate. The Division stated that if AZ's investigation of the failures showed no assignable cause, that would be acceptable, however, we are interested in knowing if any failures had an assignable cause.

Comment 4.l.(v)

Provide details of the inspection for each container closure component, including sample sizes and a description of the defects that are evaluated, and the acceptance criterion for each. Justify the AQLs for more critical attributes.

The description "inspection" in the container closure specifications refers to visual inspection. Does this request for additional information relate to visual inspection only?

Discussion:

The Division stated that our comment applies to all specifications that have AQLs. Critical attributes (visual and otherwise) should be pass/fail. These include, for example, defects that can affect performance. For example, with regard to the canister, failures shouldn't be allowed for can _____ conductivity. For example, with regard to the valve, valve actuation weights should be pass/fail. AZ stated that they are planning to do as the Division suggested, with all of the requested information in one table. It was agreed that they would provide a listing of the visual attributes.

Comment 4.I.(vi)

Specify that for component testing accepted on the basis of a certificate of conformance, you will periodically validate the results. Provide the test methods (e.g., for extractables) to be employed for this validation testing and specify the test intervals.

Does the requirement for periodic validation of information on supplier's certificates of conformance relate to supplier data, as in the example given for extractables, or does the requirement extend to the verification of materials of construction, eg, confirming that the can is aluminium and the desiccant in the sachet _____ ?

Discussion:

The Division stated that our comment pertains to supplier data, not to materials of construction.

Comment 4.I.(vii)

Provide residual particle data for the _____ canister for particles _____ and _____ in diameter.

Please note that AstraZeneca assumes that the term "nm" is a typographical error and should be "µm".

AstraZeneca interprets this as a request to carry out foreign particle enumeration in order to quantify the numbers of foreign particles present in cans prior to assembly of the pMDI (ie, before the valve is _____ to the can).

In order to provide data for residual foreign particles in the _____ canister, AstraZeneca intends to perform a one-off test for all the can batches used to manufacture the commercial scale primary stability batches. Cans will be sampled and blown with compressed air on the commercial manufacturing line in order to be representative of the normal manufacturing process. The cans will then be protected from contamination prior to testing. The methodology for this testing will be based on use of a _____ particle counter and will be adapted from the drug product foreign particles test method for particles _____:

AstraZeneca would be grateful for clarification of the size ranges for reporting purposes. The Agency has requested data to cover the size ranges _____ in diameter. AstraZeneca intends to report the data in line with the proposed size ranges in the drug product specification to allow more meaningful comparison with drug product data _____ with results reported as number of foreign particles per can.

Does the Agency agree with AstraZeneca's interpretation of this request, with the proposed testing approach and with the proposed size ranges for reporting purposes?

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Discussion:

The Division acknowledged the typographical error in the IR letter, and confirmed that the units are in μm . The Division also agreed with the proposals presented, and requested that the proposal for assessing foreign particulates in the _____ canister include multiple batches of _____ canister, if possible. AZ stated that they will perform this testing on 10 batches.

Comment 4.1.(xi)

Provide comparative information about flow resistance in the drug product used for clinical batches with that for product intended for marketing.

The flow resistance, at an air flow rate of _____ of the clinical product and the product intended for marketing (SYMBICORT _____ pMDI) is (_____) respectively, as stated in the NDA (refer to ' _____ actuator for SYMBICORT _____ pMDI' in 'P.2.4 Pharmaceutical Development – Container Closure System'). What additional flow resistance data are required by the Agency?

Discussion:

The Division stated that this response is sufficient, as these are quite low values for flow resistance. AZ stated that the standard actuator was used in the clinic and they intend to launch the drug product with the shield.

Colette Jackson, Project Manager

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/s/

Colette Jackson
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

4/12/06

INFORMATION REQUEST LETTER

NDA 21-929

AstraZeneca Pharmaceuticals LP
P.O. Box 8355
Wilmington, DE 19803-8355

Attention: Mark A. DeSiato
Director of Regulatory Affairs

Dear Mr. DeSiato:

Please refer to your September 23, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symbicort (budesonide/formoterol fumarate dihydrate) MDI.

We also refer to your submissions dated October 21, November 2, and 8, and December 8, and 27, 2005, and January 30, 2006.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We also remind you of our comments in our information request letter dated March 8, 2006. We request a prompt written response in order to continue our evaluation of your NDA.

1. The following comments pertain to the proposed drug product specifications:
 - a. These comments pertain to your proposed dose content uniformity specifications for the drug product. Revise the specifications to remove the parametric tolerance interval test
 - b. Include an additional acceptance criterion for the specification for spray pattern, i.e., a minimum criterion for the longest axis, based on your data.
 - c. Modify the specification for description of the drug product to add a criterion for drug deposition on can and valve surfaces.
 - d. Modify the specifications for each specified impurity which is not also a degradation product, for both drug substances, so that the drug product impurity specifications are not wider than for the drug substances themselves.

- e. Provide an agreement to reevaluate the drug product acceptance criteria within one year after approval of this application.
2. These comments pertain to the proposed analytical procedures in the drug product specifications.
 - a. Provide concise comparative summary data for the two sets of methods (automated and manual), for delivered dose uniformity and for aerodynamic particle size distribution that demonstrate equivalence of the two methods for each attribute.
 - b. Provide an agreement to modify your method for leakage rate to minimize the interfering factor _____, and begin collecting data for reassessment of the acceptance criteria.
3. Modify your post-approval stability commitment to include foreign particulates as an attribute, and to evaluate leakage rate at every stability timepoint.
4. Withdraw the proposed annual maintenance stability protocol, since it is a reduced protocol, until results from the first three production scale batches are completed.
5. It is noted that in the stability data for fine particle dose in your January 30, 2006, amendment, there is a decreasing trend over time even at 25°C/60%RH, and that some batches with this trend have data that are very close to the lower acceptance criterion (e.g., batches 900049F-01, 900050F-01, 900051F-01) at the 12 month time point after storage at 25°C/60%RH (see Figures 41 and 42 of the 1/30/06 amendment). Based on that trend, it appears that some data may fall below the proposed lower acceptance criterion at later timepoints. Investigate and address this issue.
6. Amend the comparability protocol for a change in canister _____ to include evidence that the _____ will bond appropriately to the canister over the shelf life of the drug product. Specify that the future supplement will contain stability data to demonstrate no change in drug product performance or other characteristics.
7. This pertains to your comparability protocol for future changes in the protective aluminum foil overwrap. Amend the comparability protocol _____ .e,
8. Update the methods validation package to include changes made in response to our comments pertaining to your analytical methods and validation reports, as appropriate. Include information supporting the integrity of the reference standards. Provide an agreement to submit lot numbers and quantities of the samples that you will submit for methods validation, when requested to submit them, as well as certificates of analysis for each sample submitted.
9. Provide concisely in graphical format, side by side, comparative summary release and stability data for all clinical and commercial batches for performance parameters (i.e., dose content uniformity and aerodynamic particle size distribution), including individual and mean data and mass of drugs on individual cascade impactor stages. You may combine storage orientations and batches for a specific presentation for these data. Provide separate graphs for each drug

substance. This may be considered an expansion of data provided in the original NDA, section P.2.1, pages 16 and 17.

10. The following drug master files (DMFs) which support this application are deficient: DMF

This list was conveyed to you by telephone on March 30, 2006, by Ms. Colette Jackson.

11. Demonstrate the physical stability of the drug deposited on container closure components after actuating canisters (e.g., in a simulated patient use manner) through most of their use lives. Perform a drop test on these canisters (e.g., from a height _____) and then examine them for dose delivery, particle size distribution of delivered dose, and for possible valve blockage. Alternative approaches to demonstrate physical stability of deposited drug may be undertaken if justified.

If you have any questions, call Colette Jackson, Regulatory Health Project Manager, at 301-796-1230.

Sincerely,

Blair A. Fraser, Ph.D
Chief, Branch II
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Blair Fraser

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NDA 21-929
Symbicort

We have reviewed your response dated March 17, 2006, to the Pharmacology and Toxicology Information Request dated March 3, 2006, and have the following comments and recommendations.

For rat studies 96195 and 96010, we have concerns about the significant differences in histopathology findings reported for the initial evaluation and reanalysis. Therefore, we recommend the following options.

1. An independent histopathologist should examine lung slides from the air-control and vehicle-control groups of rat studies 96195 and 96010 in a blinded fashion. For study 96010, lung slides from rats sacrificed at 6 months should be examined given that this data is critical for bridging from the oral to inhalation route. Documentation listing the qualifications of this expert lung pathologist as well as any type of relationship to AstraZeneca should be provided. Data should be provided as summary tables and individual animal line listings for the lung. If there are differences in the results of analyses conducted by the independent pathologist and your analysis for Study 96195 in the submission dated March 17, 2006, and Study 96010 (6-month sacrifice) in the submission dated September 23, 2005, that cannot be reconciled by the Division and impact the approval of NDA 21-929, an independent pathology working group will need to be convened.

2. As an alternative, you may directly convene a pathology working group consisting of experts in lung pathology to examine lung slides from the air-control and vehicle-control groups of rat studies 96195 and 96010. Documentation listing the qualifications of the expert lung pathologists as well as any types of relationships to AstraZeneca should be provided.

A study report for option 1 or 2 should be provided to the Division no later than May 1, 2006.

If there are any questions, please contact Ms. Colette Jackson, Project Manager, at 301-796-1230.

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/s/

Colette Jackson
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3/20/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-929

AstraZeneca Pharmaceuticals
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Attention: Liuda Shtohryn, PharmD
Team Director, Regulatory CMC

Dear Dr. Shtohryn:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symbicort (budesonide/formoterol) pMDI.

We also refer to your March 16, 2006, correspondence, received March 17, 2006, requesting a teleconference to discuss the Chemistry, Manufacturing, and Controls (CMC) Information Request letter dated March 8, 2006.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: March 28, 2006
Time: 1:30 PM to 2:30 PM
Location: via teleconference

FDA participants (tentative):

- Prasad Peri, Ph.D., Pharmaceutical Assessment Lead
- Alan Schroeder, Ph.D., Chemistry Reviewer
- Blair Fraser, Chief, Branch II, Division of Pre-Marketing Assessment I
- Colette Jackson, Project Manager

If you have any questions, call Colette Jackson, Project Manager, at (301) 827-9388.

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Sincerely,

{See appended electronic signature page}

Sandy Barnes
CPMS
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Colette Jackson
3/20/2006 04:18:30 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

INFORMATION REQUEST LETTER

NDA 21-929

AstraZeneca Pharmaceuticals LP
P.O. Box 8355
Wilmington, DE 19803-8355

Attention: Mark A. DeSiato
Director of Regulatory Affairs

Dear Mr. DeSiato:

Please refer to your September 23, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symbicort (budesonide/formoterol fumarate dihydrate) MDI.

We also refer to your submissions dated October 21, November 2, and 8, and December 8, and 27, 2005, and January 30, 2006.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The following comment pertains to the drug substance.

Provide multiple batch data for each of the proposed starting materials in the synthesis of formoterol fumarate drug substance, to support the proposed specifications and to demonstrate their qualitative and quantitative purity profiles. Include representative chromatograms of the purity profiles with known peaks labeled. Control individual impurities e.g., those present above .

2. The following comments pertain to the drug product.

- a. The change in manufacturing of the actuator will need to be submitted in a supplement after approval of this NDA. Appropriate data supporting that change, including adequate comparative performance data for drug product and CMC data for the actuator itself, will need to be reviewed and approved prior to implementing the change.

- b. The following comments pertain to your control extraction studies and leachables data.

- (i) Provide tables comparing leachables and extractables in terms of mass per canister. Include in these tables the maximum daily human exposure of each of the leachables, based upon the proposed acceptance criteria, and based upon a

3/8/06

60-actuation canister containing the amount of formulation expected at the end of its shelf life.

- (ii) Provide leachables data gathered across the proposed shelf life of the heat-stressed product to allow full and meaningful assessment of the correlation between extractables and leachables. Additionally, provide an agreement to add leachables testing to the stability testing program for the first 3 commercial stability batches of the 60 actuation presentation of the drug product. Include multiple time points across the proposed shelf life, and comparative extractable data for the same batches of components used in these stability studies for leachables. Our expectation is that in general, leachables data will be at lower levels than comparative extractables data.
- c. The following comments pertain to control of excipients.
- (i) Assess the purity profile of representative batches of polyethylene glycol for impurities that may not be controlled by the NF monograph, assess the safety of impurity levels found, and propose controls for impurities in addition to those in the NF monograph, as appropriate.
 - (ii) _____ for the HFA-227 propellant is deficient and DMF holder was notified in January 2005.
- d. The following comments pertain to the drug product specifications.
- (i) For the Aerodynamic Particle Size Distribution (APSD) specification, remove the throat from the _____ stage grouping, and control throat deposition separately _____ for better APSD control. Propose new APSD acceptance criteria for the new stage groupings and provide data to support the new acceptance criteria.
 - (ii) Modify proposed specifications for leachables, so that the limits are in terms of mcg per canister.
- e. The following comments pertain to the container closure system.
- (i) Provide a letter of authorization for the appropriate DMF for _____ with a reference to submission dates and page numbers for relevant information for your mouthpiece/actuator which was used in clinical and NDA stability drug product batches. Clarify whether specific actuator/mouthpiece colorants and resins identified in the NDA, as well as their suppliers, were those used for clinical and stability batches of drug product.
 - (ii) Batch analysis data for valve components do not provide actual extractables data for _____ components. Provide these data along with the age of the batches when tested. In addition, provide individual data for actuation weights from the valve.
 - (iii) Justify the change in canister manufacturing sites by providing or referencing stability data for multiple batches of drug product. Provide the results of testing for extractables from _____ canisters from each manufacturing site.

- f. Provide summary stability data (individual and mean data) and individual stability data, for clinical batches of drug product.
 - g. Explain occasional higher delivered doses observed on stability (e.g., _____ of label claim) which are not observed in the initial data. Indicate whether individual canisters have been observed which consistently deliver high or low doses over the life of the product.
 - h. Provide additional information about the very low outliers which were observed for stability batch 900055F-01. Clarify what differences in automated testing relative to manual testing may have caused this problem. Indicate why such an effect was limited to one batch if it reflects a problem with the method.
3. The following comments pertain to the micronized formoterol fumarate dihydrate drug substance.
- a. Characterize and control shape and surface appearance of the micronized formoterol fumarate dihydrate.
 - b. For each _____ step, indicate the quantities of all solvents, reagents and auxiliary materials used, where these have not been specified.
 - c. Indicate the test and the type of method used to determine completion of the reactions in steps _____ of the synthesis of formoterol fumarate dihydrate micronized.
 - d. Specify the limits used for micronization parameters around each target _____.
 - e. Indicate how it is determined that the conditioning operations have reached completion for the micronized drug substance.
 - f. The following comments pertain to the analytical procedures for Assay of Formoterol Fumarate Dihydrate and _____ Impurities _____
 _____ Impurities in Formoterol Fumarate Dihydrate
 _____ . Since these methods will be used for impurities at release and on stability, provide additional system suitability criteria to ensure sensitivity of the methods near the LOQ, and to ensure adequate separation of peaks.
 - g. Modify the assay and impurities : _____ to specify relative retention times and response factors for other impurities (e.g., _____ and _____). Demonstrate that this method is adequate for assay of all potential degradants and show that the process impurities do not interfere.
 - h. Modify the _____ method for impurities _____ to clarify the mobile phase used for re-equilibrating the column after the _____ is completed.
 - i. Modify the method for _____ to include a system suitability test (resolution) for the _____ peak and the drug substance peak.

- j. Modify all chromatographic methods to specify run times to ensure all impurities have eluted before the next run.
 - k. Explain how the assignment of the _____ of the formoterol fumarate dihydrate drug substance was made (RR/SS vs. RS/SR).
 - l. The following comments pertain to your acceptance criteria for impurities, _____ residual solvents, and _____ in the unmicronized formoterol fumarate drug substance. Provide an agreement to reevaluate these acceptance criteria within one year after approval of this application.
 - m. Demonstrate that the range of proposed unmicronized drug particle sizes does not affect the particle size distribution (PSD) or solid state characteristics of the micronized drug substance.
 - n. The following comments pertain to your acceptance criteria for impurities and residual solvents in the micronized formoterol fumarate drug substance. Provide an agreement to reevaluate these acceptance criteria within one year after approval of this application.
 - o. Provide data to ensure that the drug substance container and closure system is free of any residues that might transfer to the drug substance. If not, such residues should be characterized and controlled, and drug substance should be evaluated for leachables. This not only includes the surfaces in contact with the drug substance, but also any _____.
4. The following comments pertain to the drug product.
- a. Provide the details of the calculations for the target fill weights, including the following factors: weight of suspension required to deliver the target number of actuations, the number of actuations required from the pMDI for function testing and priming, fill weight variability, actuation weight variability, leakage and the amount of suspension that cannot be sampled at the end of canister life (ullage). Modify the labeled fill weight so that it is based on the lowest reasonable fill weight minus the normal amount of leakage observed over shelf life, and minus formulation weight used in 100% testing during manufacturing.
 - b. The following comment pertains to your drug product characterization studies.

In the study of delivered dose after varying periods of non-use (Attachment 1), investigate the reason for the significant increase in variability for all time points after the initial actuation following priming.
 - c. The following comments pertain to your control extraction studies and leachables data.
 - (i) Clarify the LOQ in the analytical method for _____ (Table 18, pg. 294, pharmaceutical development report) which according to the footnote "c" _____ Since the acceptance criterion for individual _____ is _____ ensure that the method is sufficiently sensitive to achieve control at this level.
 - (ii) Provide methods and their validation studies, for the leachables methods used _____, and ensure _____.

- i. The following comments pertain to drug product test procedures.
- (i) Modify the description method _____ to include evaluation of the visible surfaces of the valve after the canister is opened.
 - (ii) Modify chromatographic methods to remove the phrase “or equivalent” from description of the columns. Specific validated columns may be included. Similarly, for the method for Delivered Dose Uniformity _____, remove the phrase “or equivalent” from the listing of the validated automated dose delivery equipment.
 - (iii) This comment pertains to your impurity methods for budesonide and formoterol fumarate dihydrate. Add system suitability requirements for repeatability of injection. Clarify that all known impurities/degradation products are listed in the methods along with the approximate retention times (Table 3). For the budesonide impurity method, include a representative chromatogram of the impurity standard with all impurity and degradant peaks labeled.
 - (iv) This comment pertains to your impurity method for formoterol fumarate dihydrate. Since the retention times are so close for peaks from _____ modify the system suitability test to show adequate separation of these two peaks.
 - (v) This comment pertains to your methods for impurities. Clarify the origin and composition of each of the following: the budesonide reference standard for impurities and the formoterol fumarate dihydrate reference standard for impurities.
 - (vi) Clarify which method, automated or manual, is proposed as the regulatory method for delivered dose and uniformity of delivered dose for the two active ingredients in the drug product. Modify the specifications sheets to indicate regulatory and alternative methods. This also applies to the methods for aerodynamic particle size distribution.
 - (vii) Include in the methods for delivered dose uniformity, information about the number of actuations wasted and the specific actuations collected over the life of the can, for the various drug product presentations. For the automated dose delivery method, provide a summary description of the equipment and operation of the _____ Automated Dose Delivery System. Include reasonable upper limits on shake time (for both manual and automated methods) prior to each actuation, and with the automated method, provide assurance that shaking force does not substantially exceed that expected to be used by the patients. These comments also apply to your methods for aerodynamic particle size distribution. Provide a summary description of validated automated APSD equipment and its operation. These comments also apply to the validated waste firing apparatus utilized.
 - (viii) Correct the manual APSD method description since it refers to stages _____ in this procedure.

- (ix) For the analytical procedure for residual _____, clarify the standard preparation section. For example, clarify how the desired concentrations are achieved, and correct an apparent mistake, _____
_____ Explain abbreviations.
- (x) Modify the method for _____ (leachables) in drug product to specify which specific _____ are included in the standard solutions. Clarify that _____ is also included as a target analyte. Modify the method to include the system suitability tests and criteria.
- (xi) The following comments pertain to the system suitability tests of the method for _____ leachables. Modify the criteria for resolution so that it is defined according to USP. Include a capacity factor. Include a standard to demonstrate that the method is capable of quantifying a peak near the level of the LOQ.
- j. The following comments pertain to your validation of analytical procedures for the drug product.
- (i) This pertains to the method for budesonide impurities. Expand your evaluation of the robustness of the method, using ICH Q2B as a guide, since you have only reported solution stability as a measure of robustness. This comment applies to your other chromatographic methods as well. Provide relative response factors for known impurities and degradation products.
- (ii) This pertains to the method for formoterol impurities. Expand your evaluation of the robustness of the method, using ICH Q2B as a guide, since you have only reported solution stability as a measure of robustness. In this evaluation, also assess the separation of the budesonide impurity _____ from the formoterol impurity _____ under varying chromatographic conditions and with different columns, and for various ratios of the _____ impurities.
- (iii) Expand your evaluation of robustness of your methods for delivered dose uniformity and aerodynamic particle size distribution (e.g., as per ICH Q2B) and as part of this study, show that changes in chromatographic parameters and columns do not adversely affect the quantification of formoterol fumarate dihydrate. In this study, consider the resolution between the formoterol fumarate peak and the adjacent budesonide impurities and degradants, especially when those impurities/degradants are at their allowable upper limits for the highest strength product.
- (iv) In your comparison of accuracy for the automated vs. the manual method for APSD, it was noted that there are some stage by stage differences (e.g. a tendency towards somewhat less drug on the throat, and more on stages _____ and _____ the manual method vs. the automated method). Investigate a larger database to determine if this is a general trend, and make any necessary adjustments to the methods to diminish the differences between them.

- (v) In your study of the stability of _____ solutions in the method for _____ leachables, indicate whether the samples were stored with protection from light, and if this is necessary, add this to the requirements of the method.
 - (vi) This comment pertains to your validation data for the method for _____ leachables. Provide appropriate clarification to show that the concentration ranges (expressed as $\mu\text{g/pMDI}$) studied for each leachable are relevant to the actual expected concentrations (expressed as ppm in the formulation) of these leachables in both fill weights of the drug product.
- k. Provide summaries and individual batch release data for individual cascade impactor stages and components. Account for the failures observed in the batch release data, relative to the proposed mass balance specification.
- l. The following comments pertain to the container closure system.
- (i) Provide unique identifiers (numbers) for each container closure component.
 - (ii) Determine the qualitative chemical composition of the materials used in the container closure system, so that you may verify that all appropriate target analytes have been included in development of the analytical methods for extractables. This pertains to the compositions of the base resins as well as the compositions of the fabricated components.
 - (iii) Provide the qualitative chemical composition of the mouthpiece colorant from _____ and provide specific food additive references for each component of this colorant.
 - (iv) Provide a sampling plan for the batch analyses, as well as for the container closure component specifications.
 - (v) Provide details of the inspection for each container closure component, including sample sizes and a description of the defects that are evaluated, and the acceptance criterion for each. Justify the AQLs for more critical attributes.
 - (vi) Specify that for component testing accepted on the basis of a certificate of conformance, you will periodically validate the results. Provide the test methods (e.g., for extractables) to be employed for this validation testing and specify the test intervals.
 - (vii) Provide residual particle data for the _____ canister for particles \times _____ in diameter.
 - (viii) Provide information about the materials comprising the _____ card to be included inside the drug product overwrap. Explain the conditions needed to change the color of the _____ card and what this indicates about the desiccant sachet inside the overwrap.
 - (ix) This pertains to the method for extractables for the mouthpiece (method _____). The “sample analysis” section of the method calls for a

comparison with reference standard spectra for _____.
Modify the method to specify which _____ peaks must be present in the sample.

- (x) Develop and implement an identity test for the _____ of the overwrap _____, as part of the acceptance specifications.
- (xi) Provide comparative information about flow resistance in the drug product used for clinical batches with that for product intended for marketing.
- (xii) Provide information about the planned timetable for _____ development.

If you have any questions, call Colette Jackson, Regulatory Health Project Manager, at 301-796-1230.

Sincerely,

Blair A. Fraser, Ph.D
Chief, Branch II
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Blair Fraser
3/8/2006 12:42:07 PM

3/3/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

INFORMATION REQUEST LETTER

NDA 21-929

AstraZeneca Pharmaceuticals LP
P.O. Box 8355
Wilmington, DE 19803-8355

Attention: Mark A. DeSiato
Director of Regulatory Affairs

Dear Mr. DeSiato:

Please refer to your September 23, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symbicort (budesonide/formoterol fumarate dihydrate) MDI.

We also refer to your submissions dated December 15, 2005, and January 19, and 30, 2006.

We are reviewing the Clinical and Pharmacology/Toxicology sections of your submission and have the following comments and information request. We request a prompt written response in order to continue our evaluation of your NDA.

1. As communicated during the IND development phase, excipients, povidone K-25 (PVP K-25) and polyethylene glycol 1000 (PEG-1000), in the Symbicort HFA pMDI drug product are not found in any approved inhalation drug products. A 6-month inhalation toxicology study is required to bridge these excipients from the oral to inhalation route. Your bridging program involved chronic studies conducted with similar excipients, povidone K-30 (PVP K-30) and polyethylene glycol 600 (PEG-600).

In a 3-month inhalation toxicology study (Study 96195-1) conducted with rats that received Formoterol HFA pMDI containing excipients, PVP K-25 and PEG-1000, as found in the Symbicort drug product, there were histopathological findings in the lungs consisting of alveolar histiocytosis, pneumonitis, and congestion in the vehicle-control group that were increased in incidence and severity as compared to the air-control group. During final review of this study under the NDA, it was determined that these findings are indicative of local toxicity induced by the vehicle (PVP K-25 and PEG-1000).

Using comparable or higher doses of PVP K-30 and PEG-600 in chronic toxicity studies, there were no histopathological findings indicative of local toxicity in the lung as compared to the 3-month toxicity study with formoterol HFA pMDI that contained PVP K-25 and PEG-1000. It no longer appears that the use of similar excipient, PVP K-30 and PEG-600, to bridge PVP K-25 and PEG-1000, respectively, is a valid approach.

You can provide an explanation for the histopathological findings of alveolar histiocytosis, pneumonitis, and congestion observed in the lung from Study 96195-1 and provide historical control data for incidences of these findings in the lungs of air-control rats from inhalation toxicology studies of comparable duration from the testing laboratory or published scientific literature, although it is unclear if this would allay our concerns. Therefore, you should conduct a 6-month inhalation toxicity study in rats with PVP K-25 and PEG-1000 to bridge these excipients from the oral to inhalation route.

2. Studies 716 and 717 each evaluated a single dosage strength of Symbicort (80/4.5 mcg and 160/4.5 mcg, respectively) in an asthmatic population with a different level disease severity. We note that within the clinical program there was no within-study comparison of different Symbicort dosages.
3. Each dosage strength of Symbicort and the budesonide monoproduct represents a separate formulation, 80/4.5 mcg or 160/4.5 mcg and 80 mcg or 160 mcg, respectively. Since studies 716 and 717 each evaluated a single dosage strength of Symbicort compared to the corresponding dosage strength of the budesonide MDI, within the clinical program there was no replication of the comparison of each Symbicort dosage strength formulation against the corresponding budesonide mono-component or for the budesonide mono-component against placebo.
4. We note that the proposed to-be-marketed product was not used in the pivotal clinical studies, 716 and 717, nor was it used in the comparative pharmaceutical study 729.
5. We note that study 729 evaluated the pharmaceutical differences between the Symbicort MDI 80/4.5 mcg formulation/device and the OXIS Turbuhaler device; there was no evaluation of the pharmaceutical differences between the Symbicort MDI 160/4.5 mcg formulation/device and the OXIS Turbuhaler device.
6. Since your application was submitted, the FDA has requested manufacturers of long-acting beta-agonists (LABAs) to include a boxed warning and medication guide for the LABA component. Please submit proposed labeling with this information.

Please respond only to the above request for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Colette Jackson, Regulatory Health Project Manager, at 301-796-1230.

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Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CSO
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sandra Barnes
3/3/2006 11:50:10 AM

MEMORANDUM OF TELECON

DATE: January 11, 2006

APPLICATION NUMBER: NDA 21-929 SYMBICORT (budesonide/formoterol) pMDI

BETWEEN:

Name: Mark DeSiato, Regulatory Affairs Director
Luida Shtohryn, PharmD, Director, CMC Regulatory Affairs
Andy Ludzik, BSc, Team Manager, Analytical Development
Rob Whyard, Associate Director, Pharmaceutical Project Management

Phone: 1-866-208-4528

AND

Name: Alan Schroeder, Ph.D., CMC Reviewer
Colette Jackson, Project Manager
Division of Pulmonary and Allergy Products

SUBJECT: To discuss AstraZeneca's December 27, 2005, submission.

DISCUSSION:

Dr. Schroeder requested that the summary of stability data include graphs for delivered dose uniformity and Aerodynamic Particle Size Distribution (APSD, by stage groupings), and be organized by individual parameters. The graphs should include individual data from the batches as well as batch means. For dose content uniformity (DCU), all three storage orientations may be placed on one graph (e.g., three separate columns of data on the graph, side by side, for each time point). For multiple batches, it may be possible to combine the individual data for a given presentation and storage orientation as long as they are not substantially different. He asked that proposed limits on the graphs be included, and for DCU limits of 20%, 25%, 30%, and 35% of label claim should be indicated. He requested that there be a different symbol for each batch presented on the graph. AZ questioned if the percentage limits apply to individual delivered doses, and not batch means. Dr. Schroeder agreed. As indicated, the orientations could be displayed on the same graph, though it would be beneficial to see the life stages separately. We noted again that we do want to see all individual data points plotted, as well as batch means.

Dr. Schroeder noted that the tables of stability data should be organized by individual parameters, for individual and mean data. This should apply to all parameters, but if this is problematic, AZ should focus on the impurities, delivered dose uniformity (DDU), and APSD. For APSD, individual stages/components should be displayed. AZ asked if they need to look at both active components. Dr. Schroeder said "yes".

AZ summarized the teleconference:

1. Provide individual tabular data for all parameters.
2. Provide individual data for DDU and APSD on graphs and proposed limits. Orientations may be combined on one graph as discussed.
3. For DDU, tables may capture individual data for DDU by providing range and RSD.

We note that mean data for DDU and APSD should also be provided graphically.

AZ stated that the data and tables will contain all data to date (12 months) and they would like to make an amendment to the NDA in March 2006. Dr. Schroeder indicated that this would be too late in the cycle for review.

Dr. Schroeder asked AZ to explain the significance of the delivered dose “acceptance value” as mentioned in the December 27, 2005, amendment. $AV = |m-100| + k s$, where m is the sample mean, s is the sample standard deviation, and k is the sample size dependent scaling factor (k=1.6 for n=30 and k=1.3 for n=90). Also, he asked that they explain the negative leak rate (weight gain) reported in the stability data. AZ stated they will include their responses with their forthcoming submission of the graphs previously discussed.

Colette Jackson, Project Manager

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/s/

Colette Jackson
2/9/2006 06:02:16 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION		
TO: (Division/Office) David Hussong, Ph.D., Chief of NDMS/OPS			FROM: Alan C. Schroeder, Ph.D./ONDQA		
DATE: 1/13/2006	IND NO.:	NDA NO.: 21-929	TYPE OF DOCUMENT: Original	DATE OF DOCUMENT: 9/23/2005	
NAME OF DRUG: Symbicort Inhalation Aerosol		PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG: S	DESIRED COMPLETION DATE: 15 FEB 2006	
NAME OF APPLICANT: AstraZeneca					
REASON FOR REQUEST					
I. GENERAL					
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY _____		<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> REPOSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (Specify below) Micro accept. criteria and methods	
II. BIOMETRICS					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER			<input type="checkbox"/> CHEMISTRY <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER		
III. BIOPHARMACEUTICS					
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE					
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY			<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)		
V. SCIENTIFIC INVESTIGATIONS					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS (Attach additional sheets if necessary) This NDA is an electronic submission, available on the EDR. Please evaluate the following drug product acceptance criteria, methods and validations for microbiological quality of this MDI. (These are in Module 3 of the NDA.) Section P.5.1 proposed drug product specifications. There are 4 sets of specifications, one for each product presentation. The proposed acceptance criteria for microbiological quality are the same for each presentation. Section P.5.2 analytical procedures for the following methods: <hr style="width: 25%; margin-left: 0;"/> Section P.5.3 method validations <hr style="width: 25%; margin-left: 0;"/> Please evaluate the following acceptance criteria for the two bulk drug substances: <u>Formoterol fumarate:</u> <u>Budesonide:</u> _____ (these acceptance criteria are already approved for another NDA, an inhalation powder).					
SIGNATURE OF REQUESTER			METHOD OF DELIVERY Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER		

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/s/

Alan Schroeder
1/13/2006 03:39:08 PM

1/16/06

MEMORANDUM OF TELECON

DATE: December 13, 2005

APPLICATION NUMBER: NDA 21-929 SYMBICORT (budesonide/formoterol) pMDI

BETWEEN:

Name: Mark DeSiato, Regulatory Affairs Director
Luida Shtohryn, PharmD, Director, CMC Regulatory Affairs

Phone: 302-885-1386

AND

Name: Prasad Peri, Ph.D., Pharmaceutical Assessment Lead
Colette Jackson, Project Manager
Division of Pulmonary and Allergy Products

SUBJECT: To discuss CMC comment #2 of the Agency's December 6, 2005, Filing Review Letter.

DISCUSSION:

AZ referred to comment #2 of the Agency's December 6, 2005, Filing Review Letter:

Provide summaries of the primary drug product stability data both in tabular (include means of batch results) and graphical (include means and individual batch results) format. Separate the data by stability storage condition, test parameter and storage orientation, as well as by package size and strength. Include all time points and individual stage cascade impactor data.

AZ stated that the NDA was submitted with only 6 months of primary stability data, and they intend to submit the 12-month data during the review cycle in March 2006 to support their proposed shelf life. The Agency stated that summaries for the initial 3 batches with the rest of the data submitted in March does not allow for the reviewer to meet our Good Review Management Practices guidelines, and we need all of the data (or whatever is available) within one month or earlier. Without the data, it will be a review issue. AZ stated it would be impossible to generate the data by the end of December, for approximately 1200 graphs need to be generated. If some of the parameters could be combined on one graph, it would be helpful. The Agency suggested AZ select one batch for all of the information, and select one parameter to assess the type of plots desired. APSD and DDU are the most critical. AZ stated the earliest they could submit the information on DDU parameters would be early January. It would be approximately 400 to 500 graphs. The Agency encouraged AZ to submit the data as soon as possible, and once submitted, AZ can request a teleconference to discuss the content.

Colette Jackson, Project Manager

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/s/

Colette Jackson
1/10/2006 05:45:24 PM
CSO

12/27/05

MEMORANDUM OF TELECON

DATE: December 5, 2005

APPLICATION NUMBER: NDA 21-929 SYMBICORT (budesonide/formoterol) pMDI

BETWEEN:

Name: Mark DeSiato, Regulatory Affairs Director
Tara Chapman, Regulatory Affairs
Paula Martin, Biostatistics
Chris Miller, Biostatistics
Chris Moriak, SAS Programmer

Phone: 302-885-1386

AND

Name: Ted Guo, PhD., Statistical Reviewer
Ruthanna Davi, Ph.D., Statistical Team Leader
Colette Jackson, Project Manager
Division of Pulmonary and Allergy Products

SUBJECT: The Agency's November 29, 2005, statistical facsimile.

The Agency sent a fax to AstraZeneca (AZ) on November 29, 2005, to request information in order to facilitate the statistical review. AZ contacted the Agency to request clarification. AZ sent the following e-mail (in italics) outlining their preliminary response to the Agency, and to provide the basis for discussion. The discussion follows in normal font.

Per our conversation, please find in the body of this e-mail the talking points for the teleconference scheduled between AstraZeneca and the Division on December 5, 2005.

Following the teleconference, AstraZeneca will formally submit a response.

The bolded text signifies the FDA request with AstraZeneca's response located directly below.

Please call me if you have any questions.

- 1. Submit the analysis data sets including the primary and secondary efficacy variables (e.g., AUC and baseline-adjusted AUC of FEV1 at endpoint) that would be sufficient for conducting the primary and secondary efficacy evaluations. These data sets should not be serial FEV1 data sets. Because we are early in the review process and many details of the application are yet to be sorted out, if you have submitted such analysis data sets, please advise us how to locate them.***

For Studies 716 and 717, all analysis datasets that were used for the analysis of the primary and secondary efficacy variables were submitted in the NDA. The analysis datasets are named with an underscore prefix, in contrast to the raw datasets, which do not begin with an underscore. The datasets are located in Section 5.3.7.2 of the NDA. Within Section 5.3.7.2, the datasets are organized by Study Number. Within each study, the raw datasets are presented first, followed by the analysis datasets. Datasets are organized alphabetically within the raw and analysis dataset groupings.

For both Studies 716 and 717, the dataset “_PFT02” is the analysis dataset that contains the co-primary endpoint “baseline-adjusted average 12-hour FEV₁”. This is the change from baseline (the predose FEV₁ at randomization) in the AUC divided by time, as described in the clinical study reports (CSRs). The variable using the primary extrapolation method to handle missing values (ie, WV Pre-CF) is called “_AVGAUC2”.

For both Studies 716 and 717, the dataset “_PFT01” is the analysis dataset that contains the co-primary endpoint “change from baseline in predose FEV₁”. This variable is called “_CFEV”.

*Note that datasets _PFT01 and _PFT02 contain serial FEV₁ data; these are **in addition** to the derived variables that were used directly in the statistical analyses. A quick way to see how the analyses of these variables were conducted is to go to the Program Files folder within the Case Report Tabulations section of the NDA. Once there, select a study, and then select the “Efficacy Analysis” folder. The destination program is the code that produced the statistical analysis output in Appendix 12.1.9 of the CSR. This code is well documented and does not rely on macro functions to perform the analysis. Using this code, one can reproduce the primary efficacy analysis of the co-primary variables. In addition, the code performs several sensitivity analyses of these variables, as documented in Section 7.6.1 of the CSRs. The code will likely prove useful to the FDA Statistical Reviewer to see how AstraZeneca used the analysis datasets, described above, to select the primary variables at the primary timepoint in the primary patient populations.*

In the programs, please ignore references to the macros “RSTART” and “RSTOP” (ie, please comment out that code). As described in the program documentation, these macros are used to add titles and footnotes to the output and to name the output files; they are for internal AstraZeneca use and do not serve an analysis function.

Discussion:

The Division noted that the computer program in the Efficacy Analysis folder cannot run without calling additional macro programs that had not been found in the submission. The Division requested that AZ re-examine the program to make certain it can run independently in a different environment. AZ concurred.

The Division appreciated the clarification of the names of the primary and secondary efficacy variables used for statistical analyses.

2. ***Provide the SAS formats with which variables in the already submitted electronic data sets are formatted. This may be done in one of two ways: (1) provide the SAS programs generating the formats, (2) use SAS procedure to export the SAS format catalog to a SAS data set, then convert and submit it as a SAS v.5 transport file, in accordance with the Agency's guidance for electronic data submissions. If some formats are unique to a particular data set and cannot be shared (referenced) by others, please make proper separation and document in a clear fashion.***

Note that, in each dataset, variables that require a format have a corresponding decoded variable within the same dataset. These decoded variables are named with an underscore suffix. For example: In dataset DEM, the variable SEX_ is the character decode of the raw unformatted variable SEX. In dataset _LAB01, the variable LABCODE_ is the character decode of the raw unformatted variable LABCODE. In many cases, this convention obviates the need to use SAS format libraries to understand the data or to perform analyses.

In accordance with FDA's request, AstraZeneca is prepared to submit the SAS formats for Studies 716 and 717:

- a. *The SAS v.5 transport files are exports of the study format catalogs. They contain SAS formats assigned to the raw data (ie, site-generated or patient-generated raw data captured on the Case Report Forms or captured electronically).*
- b. *The SAS programs contain AstraZeneca-defined formats that were used in the reporting process for the studies. These formats may have been assigned or accessed in programs used to create derived variables (ie, reporting dataset programs) or in programs used to create reports/analyses (ie, summary table programs).*

Discussion:

The Division stated that this proposal is acceptable. However, if both a formatted variable and the corresponding decoded variable are already included in the data set, the SAS format actually is not needed.

3. ***Provide well document SAS programs (including ALL the relevant macro functions) that produced the primary and secondary efficacy results. Please test run these programs under SAS v.8+ before submitting them to the Agency.***

Please refer to AstraZeneca's response to question 1. The efficacy analysis programs provided with the NDA are based on AstraZeneca's understanding of the discussions with FDA at the pre-NDA Meeting. These SAS programs allow FDA to easily reconstruct the analyses of the co-primary efficacy endpoints in Studies 716 and 717.

Please confirm that FDA would like additional SAS programs, to be able to reconstruct the analyses of the secondary efficacy results. These could potentially include a large

number of programs:

- a. programs that produced secondary analyses of the primary variables (eg, at different timepoints, using different assumptions to handle missing values, using different patient analysis sets, using different ANCOVA model terms),*
- b. programs that produced analyses of key secondary efficacy variables, as defined in the CSRs,*
- c. programs that produced analyses of other secondary efficacy variables for “traditional” efficacy measures from asthma studies (eg, symptom scores, peak flow, rescue medication use),*
- d. programs that produced analyses of other secondary efficacy variables for patient-report outcomes (eg, PAQLQ(s), PSAM, MOS Sleep Scale),*
- e. programs that produced analyses of other secondary efficacy variables for patient perception of onset of effect*

AstraZeneca is prepared to submit all of the SAS programs and relevant macros used to perform all efficacy analyses (ie, those presented in Section 11.2 of the CSR). Please confirm if FDA would like all such programs or if a subset of such programs is desired, based on categories a-e, above, or any other categorization of FDA’s choosing.

Discussion:

AZ does not need to submit all of its computer programs, but for the major ones (for example, (a) and (b), in AZ’s response, above), programs are needed. AZ can use its discretion to decide which ones to submit. The Division assumes that AZ test run the programs to be submitted in advance.

Colette Jackson, Project Manager

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/s/

Colette Jackson
12/27/2005 03:33:23 PM
CSO

**DSI Audit Request for
NDA 21-929
Symbicort® (budesonide/formoterol fumarate dehydrate) Metered Dose Inhaler
(MDI)
AstraZeneca LP
Wilmington, DE**

Background

NDA 21-929 was filed electronically on September 23, 2005 (PDUFA date July 23, 2006) by AstraZeneca. The product is **Symbicort® MDI**, a new combination product of a corticosteroid, budesonide, plus a long-acting beta₂-adrenergic agonist, formoterol. The proposed indication is the "long-term maintenance treatment of asthma in patients 12 years of age and older."

The clinical program for Symbicort was comprised of 27 studies; nine of them were Phase 3. Of the nine Phase 3 studies, two are considered pivotal by the Division and they will be the focus of the audit. They are studies SD-039-0716 and SD-039-0717. In addition, we recommend that one of the Phase 2 studies, SD-039-0729, be included in this audit because it was critical to the overall program. As a combination product, Symbicort had to be compared to each of its mono-product components, but the formoterol component was only available in a dry powder inhaler (DPI) formulation, not an MDI like Symbicort. This difference in the pharmaceutical properties of the combination and mono-product was potentially problematic for the program. To help address the issue, at the Division's prompting, the Applicant conducted study SD-039-0729. This gives the study a more vital role in the overall program than might otherwise be expected of a Phase 2 study. In addition to this issue, one of the investigators in that study disclosed financial interest.

Features of the three studies which are relevant to audit activities are summarized in Table 1.

Table 1: Studies for Audit, NDA 21-929

Study & Location	Number of Centers	Number of Patients	Study Treatments	Primary Efficacy Measure
SD-039-0729: US	17	201	<ul style="list-style-type: none"> • Symbicort MDI • Formoterol DPI • (All pts also received budesonide MDI) 	Average 12-hour FEV ₁ AUC
SD-039-0716: US	63	511	<ul style="list-style-type: none"> • Symbicort MDI • Budesonide MDI • Formoterol DPI • Placebo 	Co-primaries: <ul style="list-style-type: none"> • Baseline-adjusted average 12-hour FEV₁ at Week 2 • Pre-dose FEV₁: change from baseline to average over treatment period
SD-039-0717: US	84	596	<ul style="list-style-type: none"> • Symbicort MDI • Budesonide MDI • Formoterol DPI • Budesonide MDI + formoterol DPI • Placebo 	Co-primaries: <ul style="list-style-type: none"> • Baseline-adjusted average 12-hour FEV₁ at Week 2 • Pre-dose FEV₁: change from baseline to average over treatment period

Sites for Audit

Within the three studies identified above, centers for audit were selected based on several criteria: the number of patients enrolled at the center; whether results in the primary endpoints were discrepant from other centers; and whether investigators declared financial interests. Regarding the last criterion, no investigators in SD-039-0716 disclosed financial interests. One investigator who participated in studies disclosed financial interest. He was _____ who disclosed a significant equity interest as defined in 21 CFR 54.2(b). _____ center is among those recommended for audit. _____ . No other investigators in any of the studies disclosed financial interest.

Based on the stated criteria, five study sites are recommended for audit, although because Dr. Ellis participated in two studies, there are only four geographic sites. The recommended sites are shown in the next Table. We recommend that all study patients at each site be audited since there were relatively few patients at each site.

The Table includes the endpoints of primary interest for the audit. Further specific information about the endpoints to aid in the audit process is provided following the Table.

Table 2: Study Sites for DSI Audit, NDA 21-929

Study & Center Number	Principal Investigator and Address	N at Center	Endpoints
<u>SD-039-0716:</u> 6027	Edward E. Lisberg, M.D. Spartanburg Pharmaceutical Research 126 Dillon Drive Spartanburg, SC 29307	18	FEV ₁ measurements at study visits 3 and 5 (weeks 2 and 12)
<u>SD-039-0716:</u> 6050	Sanchayita Tripathy, M.D. Clinical Research of the Ozarks 509 East 10 th Street Rolla, MO 65401	21	
<u>SD-039-0717:</u> 7026	Edward M. Kerwin, M.D. Clinical Research Institute of Southern Oregon, PC 3860 Crater Lake Ave, Suite B Medford, OR 97504	15	FEV ₁ measurements at study visits 3 and 5 (weeks 2 and 12)
<u>SD-039-0717:</u> 7014	Mark H. Ellis, M.D. Children's Hospital of Orange County 725 West LaVeta Orange, CA 92868	12	
<u>SD-039-0729:</u> 2904	Mark H. Ellis, M.D. Children's Hospital of Orange County 725 West LaVeta Orange, CA 92868	3	All study FEV ₁ measurements

For all three studies, the primary efficacy parameter was the average post-treatment 12-hour FEV₁. Therefore, the endpoints of interest for the audit are the individual FEV₁ measurements. Pulmonary function testing was done at each study visit. Serial FEV₁ measurements were made at 3 (±1), 9 (±1), 15 (±1), 60 (±5), 120 (±10), 180 (±10), 240 (±10), 360 (±10), 480 (±10), 600 (±10), and 720 (±10) minutes after treatment. For

studies SD-039-0716 and SD-039-0717, the primary analysis was based on the week 2 results (study visit 3), so that is the visit of primary interest. The last study visit was visit 5 at week 12, and that is also a visit of interest because it represents the durability of the treatment. These results should be audited.

In study SD-039-0729, the outcome measure was also average post-treatment 12-hour FEV₁, but the study design was different. This was a single-dose, 5-period crossover study, so each patient received each of five treatments once. Following each treatment, FEV₁ was measured over 12 hours according to the same schedule as in the other two studies. Therefore, each patient had the 12-hour serial measurements done after each treatment. Considering the small number of patients at the site, all FEV₁ results for all patients should be audited.

Spreadsheets listing the specific FEV₁ data for auditing from the three studies and the selected sites accompany this memorandum.

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/s/

John Gunkel
12/23/2005 08:07:49 AM
MEDICAL OFFICER

Peter Starke
12/27/2005 04:09:28 PM
MEDICAL OFFICER



FILING REVIEW LETTER

NDA 21-929

AstraZeneca Pharmaceuticals
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Attention: Mark DeSiato
Director, Regulatory Affairs

Dear Mr. DeSiato:

Please refer to your September 23, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SYMBICORT® (budesonide/formoterol fumarate dihydrate) MDI.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 22, 2005, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue:

We do not find any assessment of device reliability in your application. These evaluations are typically expected in the development of new metered dose inhaler products.

We are providing the above comment to give you preliminary notice of a potential review issue. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We have the following requests for information:

1. Provide a side by side comparison to show how micronized budesonide drug substance used in manufacture of drug product for clinical studies, compares to the proposed micronized budesonide drug substance to be used in the commercial drug product. Include a comparison of manufacturing site, method of synthesis, scale, solid state properties and test data associated with the specification.
2. Provide summaries of the primary drug product stability data both in tabular (include means of batch results) and graphical (include means and individual batch results) format. Separate the data by stability storage condition, test parameter and storage

orientation, as well as by package size and strength. Include all time points and individual stage cascade impactor data.

3. Provide summary data in graphical format to support the proposed cascade impactor stage groupings used in your drug product specifications. Plot the amount of each drug versus the individual stages, throat and filter.
4. Provide stability data for foreign particles in the drug product.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Colette Jackson, Project Manager, at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
12/6/2005 12:04:42 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 21-929

AstraZeneca Pharmaceuticals
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Attention: Mark Desiato
Director, Regulatory Affairs

Dear Mr. Desiato:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: SYMBICORT® (budesonide/formoterol fumarate dihydrate) MDI

Review Priority Classification: Standard (S)

Date of Application: September 23, 2005

Date of Receipt: September 23, 2005

Our Reference Number: NDA 21-929

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 22, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 23, 2006.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request within this application for a partial waiver of pediatric studies. We have reviewed your partial waiver request and agree that a waiver is justified only for pediatric studies in patients zero to

less than 6 years of age for SYMBICORT® for asthma since Pulmicort Respules® provides treatment for this age group and SYMBICORT® is not likely to be used in a substantial number of patients in that age group since the therapeutic benefit over existing treatments is unknown.

We also acknowledge receipt of your request within this application for a deferral of pediatric studies. We are deferring submission of your pediatric studies for patients 6 to less than 12 years of age until December 31, 2007.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. Please note that satisfaction of the requirements in section 2 of PREA alone may not qualify you for pediatric exclusivity.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/ Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Colette Jackson, Project Manager, at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, Ph.D.
Director
Division of Pulmonary and Allergy Drug Products, HFD-570
Office of Drug Evaluation II
Center For Drug Evaluation and Research

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/s/

Badrul Chowdhury
12/6/2005 12:08:01 PM

NDA 21-929
Symbicort

We are reviewing your NDA submission dated September 23, 2005, and we have the following requests in order to facilitate the statistical review of studies SD-039-716 and SD-039-717:

1. Submit the analysis data sets including the primary and secondary efficacy variables (e.g., AUC and baseline-adjusted AUC of FEV1 at endpoint) that would be sufficient for conducting the primary and secondary efficacy evaluations. These data sets should not be serial FEV1 data sets. Because we are early in the review process and many details of the application are yet to be sorted out, if you have submitted such analysis data sets, please advise us how to locate them.
2. Provide the SAS formats with which variables in the already submitted electronic data sets are formatted. This may be done in one of two ways: (1) provide the SAS programs generating the formats, (2) use SAS procedure to export the SAS format catalog to a SAS data set, then convert and submit it as a SAS v.5 transport file, in accordance with the Agency's guidance for electronic data submissions. If some formats are unique to a particular data set and cannot be shared (referenced) by others, please make proper separation and document in a clear fashion.
3. Provide well documented SAS programs (including ALL the relevant macro functions) that produced the primary and secondary efficacy results. Please test run these programs under SAS v.8+ before submitting them to the Agency.

If there are any questions, please contact Ms. Colette Jackson, Project Manager, at 301-796-1230.

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/s/

Colette Jackson
11/29/2005 01:02:13 PM
CSO

REQUEST FOR CONSULTATION

TO (Division/Office):

**Division of Drug, Marketing, Advertising and
Communication (DDMAC)
WO Bldg 22 Rm. 1400**

FROM:

Colette Jackson
Project Manager
Division of Pulmonary and Allergy Products

DATE October 31, 2005	IND NO.	NDA NO. 21-929	TYPE OF DOCUMENT N	DATE OF DOCUMENT September 23, 2005
NAME OF DRUG SYMBICORT® (budesonide/formoterol) MDI		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Glucocorticosteroid and beta-2 agonist	DESIRED COMPLETION DATE May 23, 2006
NAME OF FIRM: AstraZeneca Pharmaceuticals				

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Labeling Review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES	<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST
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IV. DRUG EXPERIENCE

<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS
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V. SCIENTIFIC INVESTIGATIONS

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
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COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

This is a request for an evaluation and review of the package insert, carton, and container labeling for SYMBICORT®. This submission is electronic only and is located in the EDR in the submission dated September 23, 2005.

PDUFA DATE: July 23, 2006

CC:

Archival NDA 21-929
HFD-570/Division File
HFD-570/Jackson

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) X MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Colette Jackson
10/31/2005 02:05:29 PM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 22, 2005

TIME: 3:00 PM

LOCATION: Food and Drug Administration/ Conference Room C

APPLICATION: IND 63,394/Symbicort/AstraZeneca

TYPE OF MEETING: CMC Advice Meeting

External Representatives:

AstraZeneca

- Matt Bonam, BSc, Team Manager, Analytical Development
- Anne Brindley, PhD, Director, Product Development
- Steve Burns, PhD, Associate Director, Product Development
- Tara Chapman, PharmD, Regulatory Affairs Manager
- Eric Couture, PhD, Global Regulatory Affairs Director
- Mark DeSiato, Regulatory Affairs Director
- Göran Eriksson, Global Product Director
- Chris Jones, PhD, Vice President, Pharmaceutical and Analytical R&D, Charnwood/Lund
- Liza O'Dowd, MD, Senior Director, Clinical Research
- Andy Rignall, PhD, Associate Director, Analytical Development
- Tony Rogers, Vice President, US Regulatory Hub
- Liuda Shtohryn, PharmD, CMC Regulatory Affairs Director
- Barry Sickels, MS, Executive Director, Regulatory Affairs
- Douglas Smith, Executive Director, Development
- Pam Smith, Vice President, Regulatory Affairs, Respiratory & Inflammation Therapeutic Area
- Rob Whyard, Associate Director, Pharmaceutical Project Management

Division of Pulmonary & Allergy Drug Products Representatives:

- Richard Lostritto, Ph.D., Chemistry Team Leader
- Brian Rogers, Ph.D., Chemistry Reviewer
- Harry Gunkel, M.D., Clinical Reviewer
- Colette Jackson, Project Manager

Background: AstraZeneca had a Chemistry, Manufacturing, and Controls (CMC) Pre-NDA meeting with the Division on November 1, 2004, that pertained to Symbicort pMDI. Based upon discussions at the CMC Pre-NDA meeting, AstraZeneca submitted a CMC submission dated December 21, 2004, which posed additional questions for the Division. The Division responded to those questions in a facsimile dated March 1, 2005. AstraZeneca submitted a Type C meeting request dated March 24, 2005, and an amendment to the meeting request dated April 1, 2005 to further discuss the CMC content and format of their forthcoming NDA for SYMBICORT pMDI. AstraZeneca submitted a briefing package containing questions to be discussed at this meeting on May 13, 2005. The Division responded to those questions by sending a telephone facsimile dated June 17, 2005 (see attachment). AstraZeneca submitted their clarifying questions via e-mail on June 22, 2005 (in bold italics). The clarifying questions submitted in the e-mail were officially submitted to the IND in a general correspondence dated June 27, 2005. Any discussions are captured directly under each response in normal font.

AstraZeneca appreciates receiving the Division's comments in advance of the meeting. We acknowledge the Agency's summary from the 01 November 2004 CMC pre-NDA meeting, and would like to clarify that items 1-3 apply to the valve performance prior to optimization of the valve manufacturing process. At that meeting, we could not agree on the robustness of the valve regarding the Agency's requirement of inline stress testing. Since that time, AZ has generated data, above and beyond the requirements of the Agency's CMC Draft MDI and DPI Drug Products Guidance Document, including data on comparator MDI products, which demonstrate the robustness of Symbicort MDI at temperatures far exceeding the labeled storage conditions. In fact, the Symbicort container closure system is the most thermally robust in comparison to other HFA MDIs tested. We are confident that we have developed and can manufacture the 160/4.5 and 80/4.5 strengths of Symbicort MDI and maintain the quality of the product during shipping/storage conditions and in patient use for the duration of the shelf life.

Discussion:

AstraZeneca (AZ) stated that the issues outlined in the summary have been addressed with the additional data provided in the briefing package. As a result, AZ believes the application is fileable and will submit the NDA in December 2005.

The Division noted that there was no Division input to the structure of the comparison study between Symbicort and the other marketed products. The comparison was not adequate from which to draw any conclusions.

Sufficient data were not submitted to show the relative performance of Symbicort at elevated temperatures to that of other drug products. It is believed that AZ is assuming that Symbicort is more robust than the others without sufficient data to support that assumption. As stated in the Agency's response to the May 13, 2005, meeting package, thermal robustness has to be established with extended studies throughout the shelf-life of the product, and comparisons made of all performance and valve-related variables. The comparison of Symbicort with other products is incomplete unless full stability data are provided through expiry.

Beginning- to end-of-canister life variability, beginning- to end-of-manufacturing run variability, and through-shelf life variability comparisons are necessary for comparative purposes. There appear to be numerous unpredictable variables and intrinsic design differences which make it difficult to establish an adequate scientifically sound comparison. AZ stated that this kind of comparison is not required for the NDA and the product will stand alone based upon their proposed comparison testing. The Division stated that AZ may not be able to perform an adequate comparison and if they cannot do a full characterization, they cannot make any claims. If the study is done, it is useful internally as a company to gain confidence of their product.

We have the following points of clarification and items to discuss with the Division at our CMC meeting on 22 June 2005:

Question 1: AZ would like to clarify that the data presented in the briefing document on the 12 commercial scale primary stability batches have been manufactured with the ~~original~~ and with valves made with the improved valve manufacturing controls (also note that the improved valve component dimension limits used are within the ranges used in the Phase III clinical product for each component). Additional dose uniformity and leakage data on these batches will be provided in the NDA.

Discussion:

The Division asked AZ what changes have been made in the valve during the manufacturing process. AZ stated that they have improved the process by tightening the manufacturing tolerance limits of the valve components, noting that all tolerances were tightened within the range of the clinical batches. The manufacturing procedure is the same and the dedicated line has the same equipment. The Division stated that AZ would still need appropriate data to link and bridge the pre-change with the post-change drug product.

Question 2: Could the Division please clarify the following issues raised in the 17 June 2005 fax:

- *what tests, if any that are not defined in the CMC Draft MDI and DPI Drug Products Guidance, are required in "overall complete characterization data".*

Discussion:

The Division responded that a complete overall characterization of the product should be done to establish quality by design, and it is up to the sponsor to determine what data are appropriate. In addition, due to the weaknesses seen in Symbicort, additional characterization beyond the draft guidance may be needed following the review of the NDA, and the Division may suggest additional studies. The Division noted that the guidance is old and that it applies to the finished article. In the case of Symbicort, the Division notes some uniqueness in its performance that may require additional characterization. Some of the suggestions may be outside of the guidance and it is not unusual for the Division to require additional work when a weakness is noted, but AZ needs to present data and make the argument strong and compelling in support of the product. The Division could not tell AZ what these studies should be but noted they need to produce robust data without any ambiguity. AZ confirmed that a lot of data was produced, which was

above and beyond the guidance and will be provided in the P.2 section of the NDA. The Division stated this is acceptable, but also noted that the comparative data from other drug products is of limited utility. It is important that the Symbicort data stands on its own since it is not possible for AZ to fully know the other products and their failure modes. It is critical that AZ fully understands and characterizes the failure modes for the Symbicort pMDI and presents these data in the NDA in order to make a case for the thermal robustness of the product.

The Division again noted that it would be impossible to list all of the data that may be necessary since no data have been received. The characterization studies will be suggested by the deficiencies seen in the data and there is no assurance that the list of studies in the guidance would be a complete list. The briefing document contained some useful data, but the Division cannot address what else may be needed without a complete review of all of the data. The Division would like to see long-term stability data on the product with temperature extremes and performance data comparisons with unaffected products at different time points to compare normal aging versus aging caused by exposure to high temperatures. The Division noted that weaknesses have been detected in Symbicort and AZ needs to examine them scientifically and determine what additional characterization data are needed. If a problem is exposed by these studies, then that question will need to be answered. The Division stated that they do not know everything about the product so they must hedge on the advice on what may be needed. AZ should consider conducting studies in a matrix fashion with a factorial design with a well-defined design space beyond where the product operates. This could cover aspects such as time, temperature and humidity to determine where the failure modes occur. AZ noted that high temperature work had been done and the valve was performing well and there was no need to repeat this testing. The Division noted that these high temperature studies were for a short period of time (i.e., the high temperature characterization is not performed on long term stability) and that they were also interested in ICH conditions and temperature cycling. AZ stated that all of this data would be provided in the NDA. The Division further noted that the current studies are not useful to repeat, but studies with Symbicort and of a similar nature may be useful.

- *“extended studies throughout the shelf-life of the product” – and that this applies only to Symbicort*

Discussion:

The Division noted that the statement applied to both Symbicort and all comparators. It is believed that the effect of temperature instability may not become apparent until the products have aged sufficiently and allowed to undergo changes inherent in storage.

- *“adequate scientifically sound comparison” – is this comparison of variability of Symbicort canisters or comparison to comparator products?*

Discussion:

The Division stated that it is comparison to comparator products.

In addition, please clarify that significant changes seen in any parameter (e.g., DDU and/or PSD) above _____ are not a barrier to approval?

Discussion:

The Division stated that until the entirety of data is reviewed, it is not possible to eliminate any submitted data as being no cause for concern. For example, if a significant problem is demonstrated with thermal stability which is supported by data from exposure to higher temperatures, then the supporting data will be used as evidence of problem that justifies a regulatory and/or scientific decision.

Because a test is not in the ICH guidelines, it does not mean it is not important. The Division stated that they could not comment on whether the changes above will be considered a barrier to approval.

The parameters of _____ canisters and actuation weight uniformity must be considered as serious a product issue as any significant change in PSD or DDU. Our data submission shows that a change for one or more of these parameters was observed for each marketed HFA MDI indicating that each product undergoes a significant change in some critical product parameter when exposed to temperatures above _____. Given the totality of the data presented on all parameters, the maximum stable temperature of Symbicort is similar to the comparators tested. We will present data in the NDA to confirm that:

- *the variability in DDU and PSD does not significantly increase due to high temperature exposure.*
- *the changes in PSD and DDU seen at extreme high temperatures _____ are not due to the valve (as shown by the totality of the data presented in Section 5).*

Discussion:

The Division noted that they do not feel that canister _____ is indicative of product performance, but rather of the construction of the components used to make the canister. They believe that DDU and PSD are more accurate measures of product performance, which would include interactions. Actuation weight is an indicator of valve performance rather than product performance, but can be used to determine the cause of a change in DDU. The Division stated that the data presented in the briefing package show substantial changes in Symbicort performance when exposed to high temperatures. These changes were greater than those seen for the comparators (see Table 16 and Table 17 of original briefing document). The Division noted that they were not going to go through each issue again in detail as the issues were clearly outlined in the fax sent in response to the questions posed in the meeting package.

_____ it is important that AZ define the failure modes for the Symbicort pMDI. If Symbicort fails at _____ there should be no cause for concern. However, if it fails between _____ there may be a problem because normal variations in the _____ temperature for the in-line stress test may cause the product to fail. AZ must use scientific judgment to characterize the product and determine where, how and when the product failure modes occur.

Question 3: The NDA will be a complete submission, including a minimum of 6 months stability data on 12 commercial-scale batches, justification of specifications, and proposed expiry dating. Submission of additional stability data was discussed with the Division on 01 November 2004, as stated in the Agency's minutes of that meeting: "The Division responded that a stability update could be provided up to 6 weeks prior to the goal date." Therefore, at a

time to be agreed with the Agency, but no later than 6 weeks prior to the goal date, AZ will update the stability data with at least 12 months data on 12 commercial-scale batches, including drug product specifications, justification, and proposed expiry dating, if applicable. In addition, AZ would like to clarify that Symbicort will be labeled with a valve-down storage orientation restriction in the supply chain (until the patient removes it from the carton). Therefore, the majority of the primary stability data is generated in valve-down storage. Data being generated on one batch of each presentation stored in multiple orientations will also be presented in the NDA.

Discussion:

The Division noted that the post-approval storage program would be based on the review of the data in the NDA and the most stability indicating storage orientation should be used post-approval. At this time, based on a preliminary review of the data, the Division noted that the valve-up storage seems to be the most sensitive as it has the greatest variability and therefore would be the most stability indicating storage orientation. The post-approval storage stability program will be based on what the data support regardless of the fact that the product is intended to be shipped with the valve-down orientation. Specifications are based on process, ICH guidance, and data.

AZ noted that the specifications will be based on valve-down storage data and questioned what specifications at post-approval would need to be met with the valve-up storage. The Division noted that there would only be one set of specifications.

AZ stated again that through the supply chain the orientation would be valve-down and once taken out of the foil by the patient the patients would not have to store in any particular orientation. The Division noted that AZ should have valve-down data, but that valve-up data should be the majority assuming it is the most stability indicating; however, this suggestion is based on limited data reviewed to date. The Division clarified that the specifications should be based on all orientations. The Division agreed that this is the normal practice, but if the performance differences in valve-up and valve-down were large then there is a robustness problem regardless of the suggested supply chain storage. Data for valve-up should not be significantly wider than valve-down and should overlap at some point with the totality of the data. The proposed specifications should be based on the worst case. Robustness should be built into the stability program and if there are not a lot of differences, slightly wider specifications may be granted. AZ noted that the valve-up and valve-down data do overlap.

AZ further noted that the primary stability protocol had 3 batches valve-down and 1 in multi-orientation and therefore there was not a wealth of valve-up data. The Division clarified that this discussion was in regard to post-approval stability and asked how much stability data had been generated. AZ noted that between 3 and 6 months data on 12 batches had already been generated; however, additional data could be obtained at the next time point. The Division noted that this data would help, but adds to the complexity and that the length of time was more important than the number of cans tested. AZ reminded the Division of the 2 supporting stability batches with 24 months of data in which some time points were missing, and the commercial scale stability batches with all

of the time points but less data, to which the Division stated that this issue can be handled by specifications and shorter shelf life. The Division further noted that the low number of batches will only be an issue if the stability batches are atypical. AZ noted the batches were primary stability batches made at commercial scale and that additional stability data would be submitted during the review cycle.

The Division then discussed AZ's suggestion of submitting additional stability data during the review. The Division noted that there was a new guidance, "Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products", issued in April 2005 that was relevant and that there had been some changes in the Agency's policy since the last meeting. The goal is to have all primary reviews completed by the end of month 8 of the initial review cycle and therefore NDA submissions must be complete at the time of the original filing. The Division may not be able to review any additional information or amendments submitted during the review. Essentially there is no allowance for development while on the review clock. The Division acknowledged that this is a new process and again reiterated that all data must be in the original submission and AZ may need to look at what date the file is submitted. They noted that this policy is being implemented consistently for all sponsors. It was clarified that the ability of the Division to review any amendments was based on workload and resource at the time. AZ stated that NDA filing plans had been built based on the agreements reached with the Division in November 2004 and this would impact the NDA filing. AZ clarified that based on the current timelines there would be 6 months data on the primary stability batches and 24 months on pilot scale data, as well as for 2 commercial scale development batches at the time of submission. The Division noted that the lack of 12-month stability data on the primary batches at filing would probably not be a refusal to file. It was also noted that the pilot scale supportive data was of limited use because it was not stress tested. In general, if 6 months primary stability data was provided and it looked great, a 12 month shelf life would be granted; any supportive 12 month data may possibly add an extra 3 months to the shelf life depending on the quality of the data. The Division stated that it is usually better for the sponsor to provide 12 months of stability data on the commercial product in the original NDA so they have a better understanding of what has been submitted. However, it remains the sponsor's decision and AZ may choose to roll the dice and submit the NDA with less data and provide additional data during the review in hope that the Division has the time and resources to review the additional data.

AZ noted that 24 month, unstressed pilot scale data were available and two 24-month commercial scale, stressed, development batches were available with limited time points. AZ further noted that the stressed commercial development batches had similar performance to the primary stability batches. It was noted that the pilot scale data should theoretically not look as good with the , but because it was not stressed the data were good. The Division noted that the non-heat stressed data were barely supportive. In fact the Division usually does not even look at stability data from unstressed product, regardless of how it looked in performance comparison with the stressed batches, except for superficial comparison with the stressed product - mainly to

determine the effect of the stress testing on the drug product. AZ reiterated that all the commercial scale batches are stressed.

AZ clarified what was needed in the NDA: ICH stability conditions on product with 3 minutes at ___ stress test and if an issue is seen then excursion work will be included. The Division confirmed that there was no need to include the high temperature comparator data and again noted that this data was good for internal use but not to make a statement or conclusion to support the robustness of Symbicort. The Division added that AZ should include whatever information in the filing deemed necessary to substantiate the robustness of the product.

AZ concluded that they had overcome the fatal flaw the Division had noted before and believed they were back to a normal valve situation. The Division noted that they had seen valve weight delivery variability, and valve problems with heat stress as indicated in their fax, and also that the variability appeared greater when stressed versus unstressed. The Division noted that concerns still existed but without reviewing the complete set of data they cannot comment and the proof should be in the NDA. AZ noted that after they received the comments in the fax they had re-examined the data that had caused the Division to see a difference in actuation weight before and after stress (Figures 3 and 11, and Table 8, actuation weight data). When the high temperature data and control data are presented together it can be shown that the variability seen is not related to heat stress. This information will be presented clearly in the NDA. The Division also noted that the end of can performance was a particularly significant issue. AZ again noted that this was not due to the heat stress, but rather normal can variability and this issue will be addressed in the NDA. AZ noted they were surprised to see actuation weight variability as an issue (Table 6) in the fax since the RSDs are very low — and compared very favorably to some of the comparator results. The Division noted changes in variability and they expect any changes to stay the same from beginning to end of can and before and after heating which is why stability information is so important. AZ stated that additional information was now available showing no change in RSD from beginning to end of can for actuation weight variability and again this information was new and therefore not presented in the package.

The Division asked AZ how close the product came to meeting the DDU requirements in the MDI/DPI guidance. AZ noted that the product could not exactly meet the limits in the guidance. AZ is able to meet the can period means at — but cannot meet — with the individual results, however a limit — can be met, or possibly a tighter specification with an outlier clause. The Division asked what the pass rate would be based on the requirements in the guidance. AZ replied that the pass rate at — is approximately in the low 90% range and that with the — limit, it is approximately a 98% pass rate at release. AZ stated that these were tentative numbers that were based on release data and data after valve-down storage. AZ also noted that it could not fully meet the Agency's guidance on the Andersen mass balance limits of + 15%, and would need a retest.

The Division noted that for PSD, all individual stage data and proposed groupings should be supplied as well as extractables and leachables and dose proportionality data. AZ noted that the fine particle mass is _____ and specifications will be proposed around a number of groupings and stages. The Division noted that if AZ were going to propose groupings it would be necessary to take the major portion of distribution and divide into groups with upper and lower limits and calculate the fractions contributing to the beginning and end tails to define the overall distribution. This is important as there may be _____ stages where the majority of the fine particle mass lies. The Division stated that this distribution is usually bimodal and the fine peak usually falls somewhere in stage _____. AZ noted that the mass balance requirement (_____) was also difficult to meet and that it was a variable result. AZ asked about the progress of the DDU IPAC-RS PTI test. The Division noted that they hope to have that guidance complete by the end of the year and that some regulatory relief will be provided by this.

AZ summarized that they understood that the high temperature excursion work was not required and that AZ believes that the valve is robust and will therefore progress with a normal P.2, and normal stability data will also be filed without comparator data. The Division clarified this was acceptable as long as no further characterization was necessary to demonstrate the robustness of Symbicort, however it was up to AZ to determine what additional data if any needed to be generated.

AZ reiterated the impact of the Agency's recent change in review practices regarding the current plans for the NDA and again noted the burden this change in the stability requirement placed on AZ. AZ added that the impact of this change would be taken back for further consideration. The Division noted this change in policy has been taken under consideration and it would be inappropriate for them to allow an amendment.

AZ stated that they believe their valve is robust and they will be moving forward with submitting their NDA by December 2005.

Minutes Preparer

Colette Jackson

Attachment: FDA June 17, 2005, facsimile to AZ.

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Drafted: CCJ/August 5, 2005

Initialed:

Rogers/August 11, 2005

Lostritto/August 26, 2005

Finalized: CCJ/ August 31, 2005

File name: 63394 junc 22 2005 cmc MM.doc

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/s/

Colette Jackson
8/31/2005 01:23:16 PM

IND 63,394
Symbicort (budesonide/formoterol) pMDI
AstraZeneca

Attached are the FDA responses to your questions and comments (in bold italics) regarding Symbicort (budesonide/formoterol) pMDI. You have the option of canceling our meeting of June 22, 2005, if these answers are clear to you. If you choose to have the meeting (or change it to a teleconference), we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan or additional questions, for which you would like FDA feedback, should be submitted as a new meeting request. Please notify the Division as soon as possible whether you are canceling the meeting.

The following is a summary of problems concluded at the November 1, 2004, CMC pre-NDA meeting:

1. Unusually Heat Sensitive System
2. Inadequate manufacturing tolerances
 - Container/closure overly sensitivity to assembly parameters
3. Thermal hypersensitivity and manufacturing issues affect
 - Patient storage and shipping
 - Increase in actuation force
 - Increase in actuation force variability
 - Valve jamming
 - Leakage at the point (time) of actuation, particularly near the end of canister life
4. Beginning- to end-of-canister dose variability for both APIs
5. Formulation physical instability
 - Loss of budesonide on stability
 - Partitioning and/or adsorption of budesonide into _____ valve components.

Sponsor Questions

Question 1: Does the Agency concur with AstraZeneca's conclusions on the suitability of the controls used in the valve manufacturing process and the approach to incoming goods inspection? (Section 4.6 Valve controls conclusions)

Agency Response

No, the changes you have made to _____ parameters and dimensional controls may also impact leak rate performance. Provide leak rate and dose uniformity data to further support your changes. In your response, include a tabulated description of all changes made to the valve and _____ which you propose.

Question 2: Based on the data presented, does the Agency agree that the perceived "materials design flaw" issue for the valve for the 160/4.5 and 80-/4.5 products has been adequately addressed and resolved and that the maximum stable temperature of SYMBICORT pMDI exhibits adequate thermal robustness and is similar to the HFA pMDI comparators? (Section 5.6 Conclusions from high temperature characterization studies)

Agency Response

No, we cannot agree at this time. The quality of the valve is a review issue once all the necessary data are provided in the NDA. We cannot adequately assess the quality of the valve, as well as the extent of the valve/formulation interactions, without review of the complete stability program data, as well as the overall complete characterization studies.

It is difficult to establish the extent of the contribution the valve materials make to the overall variability of the drug product. This overall observed variability encompasses leak rate, dose uniformity, PSD, impurity profile, etc., throughout the shelf-life. Formulation and analytical variability may also contribute to the overall variability.

Establish thermal robustness through extended studies throughout the shelf-life of the product, and comparisons made of all performance and valve-related variables. The comparison of Symbicort with other products would be an incomplete comparison unless full stability data are provided through expiry.

Provide beginning- to end-of-canister life variability, beginning- to end-of-manufacturing run variability, and through-shelf life variability comparisons. There appear to be numerous unpredictable variables and intrinsic design differences which make it difficult to establish an adequate scientifically sound comparison.

We note that there are significant batch-to-batch differences in variability at both beginning- and end-of-canister dose uniformity. For example, see Figure 11 on page 48. Exposure to _____ is not unrealistic for exposure of the drug product. Please clarify if these differences are seen in the batches without heating, with unwrapped storage at 25/60 for 6 weeks. Also address what combination of minimum heating times and unwrapped storage times do not produce such batch-to-batch variability. These differences are also seen to some extent without the 25/60 unwrapped storage as shown in Figure 3 on page 37. These differences are reflected in the valve performance (actuation weight) in Table 6 on page 33, leading to the conclusion that the differences may be related to valve performance and not formulation issues. In addition, there are significant

batch-to-batch and beginning- to end-of-batch variability induced to some extent in the fine particle dose by heating for 8 hours at —, as shown in Table 8 (on page 40). The same concerns apply to these characteristics as above related.

Comparison of Symbicort with the other marketed products show significantly greater losses for Dose Delivered and Fine Particle Dose in Symbicort than in the other drug products. For example, Table 16 (p. 59) shows that after heating for 8 hours at — there is a significantly higher change (— loss of dose delivered for budesonide and formoterol, respectively) for Symbicort than Ventolin (—) or Flovent HFA — at end-of-can. This trend is also seen at — in the end-of-can data. Also, Table 17 (p. 60) shows a greater loss of fine particle dose at beginning of canister life for Symbicort (- — for budesonide and formoterol components, respectively) when heated for 8 hours at — than that seen in Ventolin — and Flovent —. Both beginning- and end-of-can data from storage at — for 8 hours show Symbicort — loses more fine particle dose than Proventil — or Qvar —, respectively. At the higher temperatures, — Symbicort does not consistently perform better than the comparators. These comparative differences imply that there is a temperature-related loss of both delivered dose and fine particle mass in Symbicort that is not seen in the comparators. The time-dependency of these effects were not studied over the shelf-life of the products. This may alter the behavior of all these drugs to amplify the trends seen.

Question 3: Is the approach regarding submission of stability data in the NDA agreeable to the Agency? Alternatively, would the Agency prefer to have only the stability data in the original NDA and the justification of specifications, shelf life justification and statistical analysis performed with the updated stability data? (Section 7 Summary of the batch quality and stability of SYMBICORT pMDI manufactured using the commercial manufacturing process)

Agency Response

At the time of submission, provide a complete NDA submission. This includes all stability data and analyses. Amendments submitted during the review cycle may not be reviewed (see joint Guidance for Industry and FDA regarding Good Review Management Practices).

We note that the valve-up storage orientation (see Figures 24-29) appears to have the greatest variability in dose delivery, mass balance, and fine particle dose. If this trend continues, then the valve-up is the most stability-indicating and may become the required storage orientation in the post-approval stability protocol.

Question 4: Are AstraZeneca's proposals for setting the commercial shelf life in relation to budesonide concentration acceptable? (Section 7.3.2 Stability studies and shelf life strategy)

Agency Response

No. The full stability data set will have to be evaluated before any statement can be made about parameters that limit the shelf-life.

Question 5: As communicated at the 1 November 2004 CMC pre-NDA meeting, AstraZeneca will not pursue _____ in the original NDA. AstraZeneca will pursue approval of this product in a separate sNDA. Based on the data presented, AstraZeneca believes that there is no material flaw and there is no significant reason to change _____

Does the Agency concur with this proposal? (Section 8.3 Development plan)

Agency Response

No. The data are incomplete. Review of the entire set of characterization data and stability data are necessary to establish the characteristics of the container/closure and the formulation. Once this is accomplished, it may be possible to determine the portion of the overall drug product performance variability that is assignable to the container/closure, as well as its thermal stability over the shelf-life of the product in all storage orientations.

Question 6: Stability data from 3 batches of the _____ product, manufactured at the commercial scale (including stress testing), will be used to demonstrate in vitro equivalence to the Phase 3 clinical product. Does the Agency concur with this proposal? (Section 8.3 Development plan)

Agency Response

No. The adequacy of *in vitro* comparisons will depend on the quality of the 80/4.5 and 160/4.5 presentations and their variability on performance parameters over their shelf-life. This is a review issue

Question 7: Has AstraZeneca interpreted the Agency's comments on check-weighing sensitivity correctly, ie, that the check-weigh acceptance limits must assume leakage is uniform throughout the shelf-life and that for SYMBICORT MDI this means a leakage rate of approximately _____ would need to be detected in the lagging period? (Section 10.1 Detection of leaking canisters)

Agency Response

No. The check weighing after the lagging period is for detecting and rejecting canisters that are outside of in-line fill weight specifications (i.e., "gross leakers").

Question 8: AstraZeneca would like to discuss the way forward for our product as our investigations have indicated that there would be considerable technical difficulties in detecting the small weight change in a reasonable lagging period for a commercial scale process. (Section 10.1 Detection of leaking canisters)

Agency Response

Refer to our response to Question 7. The purpose of check weighing for the commercial process is to determine (and remove) any grossly leaking canisters of drug product. In contrast, as a characterization test during drug development, leak rate may be determined from individual canisters which are appropriately weighed before and after various storage times and conditions.

Responses to Agency comments

The Agency made the following comments in the fax dated 1 March 2005:

Agency Additional Comment 1

We recommend that you provide physical properties data on the currently used _____ and any proposed substitute _____ when identified. These data should include compression set, and tensile strength at _____. That data should be obtained on instruments that provide reproducible data.

AstraZeneca Response:

In the event that an alternative _____ is used for the SYMBICORT pMDI valve, AstraZeneca will provide physical property data at a range of temperatures, as recommended. Compression set is a measure applied to _____ and it is not possible to determine compression set for _____. However, AstraZeneca plan to use _____ as a measure of the properties _____ under compressive load. _____ are related measures, but it is the _____ which is of the most value in predicting performance. Data on the current _____ is provided in Attachment 1.

Agency Additional Comment 2

To support your assertion on page 2, you have not provided any examples, and we are not aware of any _____ that are routinely used _____ components in MDIs at temperatures at or above the Tg. Provide such examples to support your application.

AstraZeneca Response

_____ components of pMDI valves _____ are made from _____ that are, by definition, above their Tg at normal ambient temperature. The _____ used in pMDI valves are present as structural components _____. Attachment 1 provides a list _____ that are in common use in pMDI valves along with their Tg values, and shows that a number _____ are used at temperatures above their Tg values.

Agency Response:

We acknowledge your responses to our March 1, 2005, additional comments regarding the mechanical properties of the _____ components. Your approach appears reasonable, however full resolution of these materials issues in the drug product will require appropriate data to review in the NDA.

If you have any questions, call Colette Jackson, Project Manager, at 301-827-9388.

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/s/

Colette Jackson
6/17/05 01:57:45 PM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 1, 2004

TIME: 1:00 PM

LOCATION: Food and Drug Administration/ Conference Room B

APPLICATION: IND 63,394/Symbicort/AstraZeneca

TYPE OF MEETING: CMC Pre- NDA Meeting

FDA ATTENDEES, DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS

Badrul A. Chowdhury, M.D., Ph.D., Director
 Eric Duffy, Ph.D., Director, Office of New Drug Chemistry II
 Brian Rogers, Ph.D., Chemistry Reviewer
 Richard Lostritto, Ph.D., Chemistry Team Leader
 Peter Starke, MD, Clinical Team Leader
 John Gunkel, MD, Clinical Reviewer
 Timothy Robison, Ph.D., Pharmacology/Toxicology Reviewer
 Joseph Sun, Ph.D., Pharmacology/Toxicology Team Leader
 Sue Jane Wang, Ph.D., Acting Statistical Team Leader
 Colette Jackson, Project Manager

ASTRAZENECA ATTENDEES AND TITLES:

Tara Chapman, Pharm.D., Regulatory Project Manager
 Mark DeSiato, Regulatory Affairs Director
 Liuda Shtohryn, Pharm.D., Associate Director, Technical Regulatory Affairs
 Robert Whyard, Pharmaceutical Project Manager
 Anne Brindley, Ph.D., Director, Product Development
 Steve Burns, Ph.D., Associate Director, Product Development
 Eric Couture, Ph.D., Global Regulatory Affairs Development
 Cathy Raines, Ph.D., Head of RITA, Supply and Capability
 Andy Rignall, Ph.D., Associate Director, Analytical Development
 Douglas Smith, Executive Director, Development
 Barry Sickles, MS, Executive Director, Regulatory Affairs

BACKGROUND: The purpose of this meeting is to discuss the Chemistry, Manufacturing, and Controls (CMC) content and format of the NDA for SYMBICORT pMDI. On October 29, 2004, the Division sent written responses to the questions posed in the meeting package via facsimile (see attachment). On October 31, 2004, AstraZeneca sent their corresponding clarifications (in bold italics) below via secure e-mail and the discussion follows. **(POST-**

MEETING NOTE: AstraZeneca officially submitted their clarifications in a letter dated November 2, 2004, serial number 031).

DISCUSSION:

The Agency explained the intent of the October 29, 2004, facsimile sent to AstraZeneca (AZ), noting that the discussion will be clarification as to what was provided in the facsimile. AZ stated that they understood the Agency's intention and would like to focus upon stress testing and questions # 3, 4, 5.

AstraZeneca appreciates receiving the Division's comments in advance of the meeting. We are confident that we have developed and can manufacture the 160/4.5 and 80/4.5 strengths of Symbicort pMDI to meet the Division's requirements and maintain the product quality during shipping/storage conditions and in patient use.

We have the following points of clarification and items to discuss with the Division at our CMC pre-NDA meeting on 01 November:

Question 1 – Please clarify why this exact approach was accepted for Pulmicort Turbuhaler M3 (as agreed at the 08 September 2004 CMC pre-NDA meeting) but is not acceptable for Symbicort pMDI. We are looking for a consistent approach to submit foreign-language batch records in our NDAs.

The Agency stated that a full English translation must be provided along with the foreign language batch records. AZ stated that there are 3 executed batch records for each strength and they would like to translate one and then provide any edits for the other strengths. The Agency stated that this approach is acceptable, provided that any differences are translated and listed.

Question 2 – Data on particle size and polymorphic form – on 25 batches of unmicronized drug substance will be provided in the NDA. For particle size of unmicronized drug substance, the MMD has been monitored, and no failures of the micronized drug particle size have been seen due to the particle size of the input drug substance. For – no change in polymorphic form has been observed from unmicronized to micronized drug substance. Therefore, we would like to discuss the relevance of the particle size and – testing of unmicronized drug substance.

The Division explained that control with three points (e.g., M25, M50, M75) in the distribution would be required because characterization of the input material and monitoring of the means would not give the full picture. Changes can occur after micronization and it is common for the manufacturer to condition batches to re-establish crystallinity and minimize the amorphous content. Control of the bulk drug substance at three points in the distribution rather than just the MMD is required as the drug substance could have the same mean, but widely varying distributions. If the input particle size distribution changes from that seen in these early batches, the product may not pass specification after conditioning. The Division noted that they have seen cases where the PSD has changed the morphology and the degree of crystallinity that comes out of the micronizing process. The Division stated that once AZ gained enough experience with

this testing (e.g., after 80 batches) a proposal with supporting data could be submitted post-approval in a prior-approval supplement to justify the removal of this requirement for testing for the unm micronized drug substance.

Questions 3, 4, and 5 – We acknowledge the Division’s comments. We have had conflicting information from the Agency regarding stress testing (reference Dr. Tim Marten’s conversation with Drs. Nasr and Lostritto, as referenced in our 12 October 2004 submission) and have been encouraged (through ongoing dialogue between Dr. Marten and Dr. Ajaz Hussain) to revisit with the Division the stress testing requirement. Given these interactions, we request a general discussion to understand the Agency’s position on the usefulness of stress testing, its purpose, and the temperature required for what purpose (e.g. leak testing).

We are confident that we have developed and can manufacture the 80/4.5 and 160/4.5 strengths of Symbicort pMDI to withstand the Division’s stress testing requirements, _____ prevents the deformation of the valve. As stated on page 63, section 6.2.4.1.1, “To achieve acceptable valve performance with valves stressed at _____ additional valve controls have been implemented _____ ! These changes have given acceptable performance for SYMBICORT pMDI 80/4.5 and 160/4.5.” Also, as stated on page 75:

_____ to the same extent and consequently valve performance is acceptable even after stress testing at _____ ” We are also confident that the 80/4.5 and 160/4.5 products will withstand probable use/storage/shipping conditions. To further support the viability of the 80/4.5 and 160/4.5 products, we would like to clarify the points in the briefing document highlighted by the Division:

“... when the valve components are heated to above their Tg _____ increased deformation leads to interference _____ which can affect the smooth operation of the valve.” (Section 6.2.4.1.4.1)

“... for batches where the variability in unstressed actuation weight performance was lower (eg, batch 9100-00), stress testing had no impact.”

“... the impact of stress testing could be significantly reduced by tightening the tolerances of the valve components...” (Section 6.2.4.1.4.3)

“...By controlling the quality of the components used to construct valves, improving release procedures _____ of the product, it is possible to routinely produce stress tested SYMBICORT pMDI units that have acceptable performance.”

Deformation of the valve is dependent on a combination of temperature and load placed on the valve. Please note that Figure 11 (page 81) is on product manufactured with a _____, whereas the 160/4.5 and 80/4.5 strengths, intended as commercial products, use _____

places a load on the valve that causes deformation at temperatures above (which is above the Tg).

A comparison of Table 12 (page 69) and Table 15 (page 73), shows no statistical difference in actuation weight variability between clinical SYMBICORT pMDIs and commercial product stressed at with a demonstrating equivalence between clinical and commercial (stressed at) product.

Data in Table 14 (page 72) represent valves which we had used earlier in the development process. Since then, we have worked with to improve and optimize the valve manufacturing process to produce valves that more consistently withstand the stress testing (illustrated in Table 15, page 73). We continue to work with such that unacceptable batches (e.g., batches 50511-00 and 50509-00 in Table 15) will not be manufactured by the supplier and would therefore not need the incoming goods test described on page 73.

We acknowledge the Division’s comment “Heat stability under possible storage and shipping conditions is a critical requirement for drug product design”. Given the stability data plan presented in the pre-NDA briefing document (Table 41, pages 126-127), and the temperature cycling and the testing on pMDIs used in clinical studies, both presented in the End-of-Phase-2 briefing document (Volume 1, page 111), please clarify that the proposed studies and stability data (as reproduced below) will be sufficient to fulfill this requirement:

- Long-term stability at 25 °C/60% RH, as indicated in the table below
- Accelerated stability (up to 6 months) at 40 °C/75% RH
- Temperature cycling 4 times in each 24 hour period, for 6 weeks. The following tests will be performed at the end of the 6 week temperature cycling period:
 - Description of primary pack and can contents
 - Aerodynamic particle size distribution
 - Microscopic evaluation
 - Dose content uniformity within batch and through life
 - Water content
 - Leakage rate
 - Weight loss
- Testing on pMDIs used in clinical studies
 - Dose content uniformity
 - Aerodynamic particle size distribution

Estimate of available stability data at NDA submission

<i>Strength</i>	<i>Pack size</i>	<i>Manufacturing site (scale)</i>	<i>Stress Test</i>	<i>Orientations</i>	<i>Data planned for NDA (months)</i>
160/4.5	120	Charnwood (100 kg)	None	3	36
160/4.5	120	Charnwood (100 kg)	None	1	36
160/4.5	120	Charnwood (100 kg)	None	1	24

160/4.5	120	AZDP (850 kg)		3	6
160/4.5	120	AZDP (850 kg)		1	3
160/4.5	120	AZDP (850 kg)		1	3
160/4.5	60	Charnwood (300 kg)	None	1	9
160/4.5	60	AZDP (850 kg)		3	6
160/4.5	60	AZDP (850 kg)		1	6
160/4.5	60	AZDP (850 kg)		1	6
80/4.5	120	Charnwood (100 kg)	None	3	36
80/4.5	120	Charnwood (100 kg)	None	1	36
80/4.5	120	Charnwood (100 kg) ^a	None	1	36
80/4.5	120	Charnwood (300 kg)	None	1	9
80/4.5	120	AZDP (850 kg)		1	6
80/4.5	120	AZDP (850 kg)		3	6
80/4.5	120	AZDP (850 kg)		1	3
80/4.5	60	Charnwood (300 kg)		1	6
80/4.5	60	AZDP (850 kg)		1	3
80/4.5	60	AZDP (850 kg)		3	1.5
80/4.5	60	AZDP (850 kg)		1	1.5

^a Contains budesonide drug substance batch that was manufactured at AZDP and released against the specification in compliance with Ph Eur. The drug product batch manufactured with this drug substance batch complies with the current product specification at release and on stability, and can be considered as representative for the product.

AZ referred to conversations held between Dr. Marten of AZ and Dr. Nasr, Dr. Lostritto, and Dr. Hussein of the Agency. The Agency acknowledged the conversations, but strongly suggested that AZ operate within the appropriate procedures for a teleconference as outlined in the guidance document *Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products*. This will assure that the flow of information is consistent and official minutes can be captured and placed on record. AZ agreed.

AZ stated that they have addressed the valve performance issues and with the introduction of stress testing, _____ on the product to address unacceptable performance. AZ stated that they will focus on just the two strengths _____ and asked the Agency if the NDA would be fileable and approvable with those formulations.

The Agency stated that the requirements for fileability and approvability are significantly different, and though the application may be fileable, it is clear from the data provided in the briefing package that the valve has a design defect in the components' materials of construction. Because of inappropriate materials, the valve _____ components suffer from heat stress deformation. The Agency strongly suggested AZ change the valve components materials of construction to increase the likelihood of approval of the product. The Agency explained that it is not normal to make changes in a vital piece of the drug product, such as the valve, since it may affect the development program. If the modified valve is introduced, AZ would need to perform *in vitro* studies to link the earlier studies with the new studies. The Agency stated that if AZ decides to _____ pursue the 2 _____ strengths, then they would have to deal with this clinically as well. The Agency's intention would be to work with AZ to obtain an appropriate drug product.