

AZ stated that the current valve problem was with dose delivery due to temperature and load. AZ therefore would like to proceed with the 2 strengths, and questioned if the Agency deems it acceptable to proceed with the current valve, with data to support the two strengths.

Dr. Lostritto noted that this was a “tricky situation” and it was difficult to answer as the Division had reviewed a lot of AZ’s data presented in the briefing document, but not all the data was available on which to base their response. The Division stated that AZ would likely see problems with the product down the road and see failures with the valve due to the fatal design flaw. Issues with the valve such as jamming, sticking, leak rate, and side-streaming would likely be continuing problems. The Division indicated that was the problem, then it is recoverable, but they feel there is a material flaw, which is a fatal flaw. The Division continued by stating that the materials used in the valve were more of a problem than the valve design itself and that AZ should fix it rather than try to accommodate the current valve. The Division reiterated their concern with the current valve being able to withstand “typical patient use”, e.g. storage in hot automobiles, purses, hot mailboxes, shipping, etc.

The Division would like AZ to eliminate the root cause of the failures, which is a properties issue, and address it rather than accommodate it. This may be accomplished by picking a material with an appropriate Tg (glass transition temperature). The Division also noted that it would not be appropriate to address these issues, e.g., probable use, shipping, and storage, through product labeling since that would be vastly different from labeling on other products of this type. AZ indicated that the labeling would be the same as other MDI products – controlled room temperature, which allows for excursions to

Dr. Lostritto added that AZ should select appropriate materials of construction to avoid such problems, as this was the first time the Division had seen such a weakness in an MDI. The Division then went on to indicate that every other valve, used in both CFC and HFA MDIs, can withstand the stress testing temperature and that some, if not most, actually perform better after heat stress testing because the components become better seated after exposure to the in-line stress temperatures. The problem with the AZ product is unique and is fixable, because no other valve has this problem. The Division again noted that it may be a straight material change and that they would be open to discuss the *in vitro* comparisons that would be necessary, and reiterated that the Division would work with AZ to minimize delays in the development program if AZ chose to change the valve material.

Dr. Chowdhury stated that the Division had indicated their concerns and that several times it was stated that they see a fatal flaw, which is a difficult task to justify and overcome. Dr. Chowdhury explained that “fatal flaw” is not the type of language that the Division uses often and that it should be taken seriously. He understands that AZ is trying to get the product to the market as soon as possible, but the Division clearly sees that as a very difficult task with the current product and believed that the easiest way forward would be to change the valve.

AZ asked the Agency how could they salvage the current product, and would like to know what additional information or studies are necessary to move forward without changes to the product.

The Agency stated that realistically, additional testing under standard protocols will not alleviate our concerns about the poor valve temperature stability. The stability of the drug product is doubtful under foreseeable in-use storage conditions, and the Agency has serious concerns about approving this product prior to review of characterization data (i.e., pharmaceutical comparability, PSD before and after, DCU, leachables/extractable, leak rate, etc).

The Division then noted that AZ needs to understand that with the current valve it is unclear what additional characterization studies may be necessary to mimic patient use and shipping, specifically through the mail. Normally, the Division is not as concerned with these things, but with this product they have doubts and serious concerns under these probable conditions (i.e., an afternoon in a mailbox during the summer, or purse, or in a hot car all day). The Division indicated that this issue is unique in that they have not seen a similar flaw in other valves. Accordingly, they may require additional testing to be done in order to assure them that the design issue does not affect temperature stability under foreseeable shipping and in-use conditions. The Division has grave concerns and would be hesitant to approve such a product without further stress testing characterization studies.

The Division continued to explain their position and stated that if AZ chose to change the valve material, comparability tests, specifics of which would require additional internal discussion, would be needed to show standard performance characteristics and demonstrate *in vitro* pharmaceutical comparability such as dose content uniformity and particle size distribution before and after stress testing, extractables/leachables before and after stress testing, leak rate, etc.

AZ asked if the Division could clarify what further characterization studies may be needed if the current valve was progressed. The Division responded that general heat stability and assessments of beginning- to end-of-canister dose and other performance characteristics were likely to be important, but that they would need to have further internal discussion. AZ asked specifically what temperatures would be required for such testing. The Division responded that we could not answer that question now, as we would need to review the data in more detail before making a recommendation.

AZ stated that they had shown the good and bad information in the briefing document with the intent to change the stress testing requirement, but if they provide satisfactory performance with the current valve based on NDA stability data, accelerated stability data and temperature cycling data with what the Division knows about the PBT valve, why will the Division require work that is above and beyond the requirement for a normal MDI? The Division responded that they would not be asking anything above and beyond what would usually be required if thermal performance issues were identified.

The Agency indicated that AZ should realize that they took the appropriate steps by including all of this information in the briefing document. We indicated that it was good that these issues were being addressed now because with these T_g data in the NDA a red flag would have been raised and it would have led to serious problems with the review and approvability, which would have

been a bigger issue. He added that this issue would have certainly been uncovered during the review and probably resulted in delay in approval. At this stage the Division would like to help AZ come in with an NDA that was approvable. The Division also noted that whatever information the sponsor has regarding the history of the product development should be presented in the Pharmaceutical Development Report in section P.2. of the NDA. This will allow a science based view in which the Division can follow the development program and the logic used by the sponsor. Dr. Duffy noted that since inception of these pharmaceutical development reports, they have dramatically improved and when a high quality pharmaceuticals development report is received it helps in the approval decision and identifies critical versus less critical issues, which can lead to more rapid approval. This report is a tool, which helps the Division understand the approach of quality by design and also enables the Division to gain the sponsor's understanding of the product and gives the FDA confidence that the sponsor knows what they are talking about.

AZ acknowledged the Agency's suggestions, and stated that they understand that they are taking a risk of using the same valve.

AZ asked the Agency if they progress with the current valve and submit the stability data (pilot scale data, some stressed) at filing, would this be sufficient. The Agency stated that full scale stability data is preferred, but supportive data is acceptable. Pilot scale and shelf life data would not be supportive at filing. AZ stated they could provide additional data at the time of the action letter. The Agency noted that this is not helpful, since data is needed to generate approval of the product. The Agency stated that AZ's options would be to have the data sent after the action, prompting an additional review cycle or submit data within 3 months of the PDUFA action date and extend the review clock.

Question 6 – Our current understanding is that the IPAC-RS and FDA working group on DDU is considering a 2nd tier test for life stage means. If this becomes part of the PTI test, please clarify that we would be able to apply a 2nd tier test for life stage means.

The Agency noted that there are current internal discussions in regards to the 2 tier testing, and there may be a long time before implementation within the Agency. This can be discussed at a later date.

Question 9 – Please confirm that the colors are acceptable, based on no response to this question from the Division.

The Agency referred AZ to the facsimile sent on October 29, 2004. The Division confirmed that they had no concerns at this time.

Question 10 – Given the Division’s response to this question, we intend to launch the product with the shield actuator. Please confirm that the Division accepts the filing of the shield actuator in the NDA based on the mechanical testing and in vitro comparison data to the SYMBICORT pMDI (standard actuator) product.

The Agency noted that AZ should make sure there are no changes in the performance parameters

_____ , and the Agency warned AZ to be mindful of any changes.

Additional Comments:

Comment 2 – Please clarify that “critical batches” are those used in the pivotal clinical safety and efficacy studies.

The Agency stated that the stability batches (and supportive stability batches if they too are critical and/or important) are also critical batches of concern.

Comments 4, 5, and 6 - In regard to Dose Proportionality (3.2.39) – AstraZeneca submitted this information in response to the Division’s issues raised at the clinical End-of-Phase-2 meeting, held on 02 April 2002. This information was not planned to be submitted in the NDA. Please clarify what is required for the NDA regarding the dose proportionality information submitted 03 May 2002.

The Agency stated that the NDA could possibly reference the End-of-Phase 2 meeting data, but noted that additional data was needed based upon the data presented at that meeting. The Agency stated we would check into the requirements, and get back with AZ. (POST-MEETING NOTE: Since additional data is needed, it is advisable to submit the dose proportionality information submitted on May 3, 2002, with the additional data to the NDA.)

Comments 5 and 6 – All dose uniformity and particle size testing of Oxis Turbuhaler M2 uses controlled flow conditions. If required for the NDA, please clarify the flow rate required for PSD and DCU for Oxis M2 in Comments 5 and 6, specifically, the fixed volume of air (4L) at 28.3 L/min for PSD.

Turbuhaler M2. In addition, please clarify the range of flow rates _____ for DCU. Our usual practice is _____

AZ then asked the Division to clarify why a flow rate of 28.3 L/min was required for the Andersen CI, since AZ routinely used flow rates of _____ to characterize particle size distribution of the Turbuhaler. The Division recommends 28.3 L/min, as this translates to

approximately 30 L/min but noted that AZ could make a case for what would be relevant in the Pharmaceutical Development Report.

AZ also stated that normally flow rates of _____ are used to characterize the delivered dose from the Turbuhaler. The Division responded that _____ would usually be considered an excessive flow rate. Since the patients of interest have compromised lung function the Division usually likes to see flow rates of 20, 30, 40, and 60 L/min. AZ noted that the vast majority of patient using the Turbuhaler produced flow rates around _____ and that generally flow rates were not below _____. AZ stated that the Turbuhaler device is able to deliver appropriate doses at these flow rates.

The Division indicated that normally the sensitivity increases as the flow rate decreases and that they like to establish the lowest flow rate, even if the flow rate was below that which most patients produce, since there is, by necessity, a compromise between duplicating patient capability and measurement capability to determine product quality.

The Division continued by explaining that this ties into dose proportionality since an increased flow rate may lead to increased deposition. An important factor for DPIs is the inspiratory flow, as it not only pulls the drug out of the inhaler, it also disperses the drug and the extent of dispersion is sensitive to air flow. Agglomeration can be a problem with DPIs, and this type of problem may only show up with abnormal particle size distribution results.

AZ then clarified that for Oxis Turbuhaler M2 the Division would like to see data produced at a flow rate of _____. The Division noted that they wanted to see data produced with flow rates as low as _____ and also indicated that they were not necessarily expecting good data at _____. If low flow rates caused performance to degrade, it would not be used against the product, it would simply be used for product characterization purposes.

Comment 7c – Justification for a lagging period will be provided in the NDA. Please clarify that a shorter lagging period can be justified by data and a lagging period of at least three weeks is not required.

The Division noted that the requirement for a 3 week lagging time was based on science and that if a product was manufactured, stress tested, check weighed, equilibrated for 3 weeks and then check weighed and valve performance tested, the validation data showed that 3 weeks was generally the period of time needed to detect any change in product performance.

AZ noted that they had done work, which showed that a lagging period of 2 weeks versus 3 weeks was equivalent and that when the products were tested for dose content uniformity and valve performance they performed the same.

The Division questioned if AZ was certain that there was no leakage or if we were not able to detect leakage due to the short lagging time. AZ confirmed that they had not seen leakage and there was a lot of stability data to justify this proposal. The Division asked what the estimated annual leak rate was for Symbicort. AZ responded that the estimated leak rate was around _____. The Division noted that such leak rates were very good but that AZ should be

careful because the Division will require the ability to detect in 2 weeks what will need to hold up over the shelf life of 1 or 2 years. The Division gave the example that if a product leaked 365 mg/year, then in a 3-week lagging period the MDI would only leak 21 mg. The Division stated that generally most other MDI manufacturers can justify 3 weeks to find the leakers and optimize performance and stated that it may in fact be more beneficial for AZ to have a longer lagging period regardless of whether or not AZ was able to validate a 2-week lagging period.

Comments 8 and 9 – Please clarify the need for a fumarate specification for both drug substance and drug product. Could the drug product specification be “if tested will meet”?

AstraZeneca looks forward to discussing these issues with the Division.

The Division asked if AZ limited a batch of drug product to one batch of drug substance, since typically multiple batches of drug substance go into a single batch of drug product. AZ needed to confirm the procedure. Since fumarate is very important to the drug substance performance, the Division stated that if one batch of drug substance was used to manufacture a single batch of drug product, AZ should propose eliminating this requirement and it would become a review issue. The Division asked for AZ to follow-up on this issue with more detail.

Additional Discussion

AZ then asked if the valve issue could be discussed further with regards to stability data. AZ stated that if they chose to progress the NDA with the current valve, given the amount of stability data in the response to the FDA fax and assuming everything else stacks up, is that NDA fileable? Specifically, AZ has stability data on pilot scale, non-stressed batches from Charnwood, stressed commercial scale from AZDP, and 2 supportive commercial batches, stressed, from AZDP that were used in clinical trials.

The Division stated that we believe that AZ is in a very weak position without more stability data on product batches stressed at —. The Division stated that non-stressed stability data were of poor value regardless of batch size and that stressed batches, as close to — commercial scale as possible, were significantly more valuable. Furthermore, the most value would come from product stressed at — at full production scale, but that it was understood that supportive batches would need to be used.

AZ stated that there were data available on 2 batches of commercial scale product, stressed at — and used in the clinic. However, since these batches were not originally intended to be primary stability batches, they were not tested according to the current stability protocol, i.e. some time points would be missing. The Division noted that these data would be helpful in making comparisons, and that it may be acceptable if some data points were missing, if the same validated methods and same storage conditions were used. Of course, the value of the data would depend on the identity of the missing data points. It was stressed by the Division that full stability data with product at commercial scale, stressed at — will provide the best and most relevant data.

AZ then asked if they could file the NDA with less than 1-year stability testing on commercial-scale batches and qualified that some batches would have 6 months and some would have 3 months testing available at the time of the filing. The Division noted that with less than 1-year commercial scale stability there would be a poor chance that we could approve a workable expiration dating period. AZ asked if they could provide additional data at the time of the action letter. The Division noted that it was their objective to approve products during the first review cycle and that AZ could provide stability data during the review period. The Division noted that if AZ intended to provide additional stability data during their review the timing should be discussed and agreed with the Division prior to submission of the NDA. AZ asked how far into the review cycle would the Division accept stability data. The Division responded that a stability update could be provided up to 6 weeks prior to the goal date.

The Division then noted that AZ had encountered problems with the valve sticking _____ and questioned if after this change whether there were any intermittent issues that came up in the stability studies? AZ responded that there were no performance problems with the 2 _____ strengths (160/4.5 and 80/4.5) in the stressed batches _____. The Division clarified that we asked the above question to establish that the stability data showed that the changes solved the intermittent valve function problems. AZ replied that yes, _____ the problems had disappeared as demonstrated with both room temperature stability data as well as accelerated data. The Division then asked when the problem first appeared. AZ replied that the problems were noted in the development batches _____ after 6 weeks of storage and on release testing. This resulted in a chain of investigations, which led to _____ the current stability data.

The Division also questioned if AZ failed a significant number of valve batches. AZ replied that initially some batches failed, but that we were working very closely with _____ the valve supplier, to improve the incoming goods and that the current pass rate is approximately 85%. AZ noted that they are working with _____ in an effort to improve this pass rate. The Division asked if AZ had any problems with the _____ any tops popping off, to which AZ replied that they had not seen any such problems _____

The Division asked when AZ intended to file the NDA. AZ replied that submission was scheduled for end of 2nd quarter 2005. The Division asked if all the stability batches have been made. AZ noted that some have been and some have not. The Division restated our recommendation to change the valve composition, as we believe a change at this point would not lead to a loss in a large amount of stability data, and may lead to a minimum delay of 6 to 9 months. However, if AZ elects to file an NDA with the current product and if all of the "ifs" fall into place, the NDA may be in good shape, but this is not what the data AZ has shown leads the Division to believe. The Division feels that a decision to change the valve at this time will still leave AZ in a recoverable spot.

Colette Jackson, Project Manager

Attachment: October 29, 2004, facsimile sent to AstraZeneca.

**Appears This Way
On Original**

IND 63,394
Symbicort (budesonide/formeterol) pMDI
AstraZeneca Pharmaceuticals

Attached are the FDA responses to your questions (in bold italics) regarding Symbicort (budesonide/formeterol) pMDI. You have the option of canceling our meeting of November 1, 2004, if these answers are clear to you. If you choose to have the meeting (or change it to a telecon), 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.

Question 1: Drug product executed batch records (presented in Section 5.1)

AstraZeneca proposes to include the following documents as drug product executed batch records (EBRs) in the NDA submission:

- ***Copy of EBR (in French) for 1 representative batch per product containing all process steps***
- ***Translated unexecuted batch record for 1 patch per product containing all process steps.***
- ***Translation of comments in the form of text in the EBRs.***
- ***Translated deviation reports.***

Does the Agency concur with this proposal?

No. Documents in foreign languages must be accompanied by accurate and complete English translations [(314.50(g)(2)).

Question 2: Specifications for formoterol fumarate dihydrate and formoterol fumarate dihydrate micronized (presented in Section 6.1.6)

The test items identification by — diffraction, color of solution, heavy metals, particle size and microbial limit have been omitted from the specification for formoterol fumarate dihydrate since they are controlled by the specification for formoterol fumarate dihydrate micronized.

Does the Agency concur with this proposal?

No. The particle size and polymorphic form of the formoterol fumarate dihydrate should be controlled to assure batch-to-batch reproducibility of the material to be micronized. This material should be controlled with three points in the distribution to provide adequate control of the PSD.

Question 3: Proposal for stress testing at (presented in Section 6.2.4.1)

AstraZeneca has shown that the unstressed check-weighing process, used in clinical manufacture, is equally effective at culling marginally sealed canisters as stressing at and that it does not adversely affect SYMBICORT pMDI at the start of its shelf-life. However, based on the previous discussions with the Agency it is clear that a stress test is desired and therefore AstraZeneca proposes an in-line stress condition of

Does the Agency concur with this proposal?

No. As stated at the EOP2 meeting for this product, the stress test immerses the canisters and valve for a sufficient time to bring the equilibrium internal temperature of all canisters to at least

This heat stress testing serves multiple functions including; identifying gross leakers, seating the components of the container closure system for proper function, and providing some exposure of each unit to probable use/storage/shipping conditions,

The proposed stress testing method must be appropriately validated.

If the drug product is water sensitive, as we conclude from your use of protective packaging, an alternative mode of heating is likely to be more suitable and should be adopted.

Question 4: Switching to a stress condition from the next time point for stability studies with batches manufactured at the commercial site (presented in Section 6.2.4.1)

In advance of the pre-NDA meeting, AstraZeneca has set down stability studies on batches of SYMBICORT pMDI made at the commercial manufacturing site and scale.

For SYMBICORT pMDI 80/4.5 and 160/4.5, parallel samples from the same batch have been stressed (See Table 1). The stressed product is currently the lead product being tested on stability. For the stressed samples, all batches have been characterized at the initial time point, set down on stability but are currently not routinely analyzed. A number of unstressed control samples have also been included. Based on the proposal for a stress test for commercial process, AstraZeneca proposes to switch to testing samples stressed at from the next time point. The shelf life for the stress testing commercial will then be derived from a

*combination of the data generated up to the current time point on samples stressed at
— and the data generated at future time points for samples stressed at —*

Does the Agency concur with AstraZeneca's stability proposal?

No. If the product cannot withstand this testing based on material failure (e.g., low Tg's), it indicates that there is a serious design flaw in the container/closure system. We suggest you investigate the cause of this instability and modify your container/closure to permit this product to be shipped and stored as is common in the hands of patients.

Modification to container/closure component(s) will require reevaluation of the drug product stability and performance characteristics by further *in vitro* testing, but may ultimately prove to be a more effective course of action.

You make the following statements in your meeting package:

*"...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."

From the totality of information provided in your background package, it appears that you attribute the thermal instability of your container/closure to the valve component composition, inadequate valve manufacturing tolerances, and sensitivity of the container/closure to assembly parameters. We strongly suggest that you work v — to address all sources of variability they have control over.

Although you propose to eliminate highly variable valves by testing, it is unacceptable to have inadequate controls on their manufacture and composition so that this testing is required. Variability of this nature is best controlled at the source. Excessive testing may be viewed as "testing into compliance".

force), or possibly just an expected result (no more drug near the end of canister) as would be seen with valve jamming or leakage. Leakage that only caused an increase in dose per actuation would be a serious issue since the product may become more concentrated and provide increasing dose per actuation without any notice to the patient.

Question 5: Switching to a — stress condition in the future, if required, for stability studies with batches manufactured at the commercial site (presented in Section 6.2.4.1)

If a significant change or out of specification result is observed during the stability program that can be attributed to the — stress condition, AstraZeneca considers this as additional supportive evidence for the — stress condition adversely affecting the product performance. If this occurs, AstraZeneca intends to alert the Agency and provide a full evaluation of the relevant data to the Agency in the form of a briefing package. Based on these data, AstraZeneca would propose to switch to a — stress condition for commercial production and to switch the stability studies to testing at as discussed in Question 4.

Does the Agency concur with this proposal?

No. Fallback to the — canisters is unacceptable. If there is a significant change in stability as a result of stress testing at — discussion with the review Division will be necessary to agree on the focus of a follow-up investigation. It is likely that a change in container/closure will be necessary to solve this stability problem.

The use of in-line stress testing has been an expected industry standard test for many decades and was not implemented as a practice with the MDI/DPI draft guidance, as you state in Section 6.2.4.1.2. Therefore, the timing of your submission to the appearance of this point in the guidance is not relevant.

Considering the temperatures encountered in day-to-day usage and during shipping via mail over time spans of hours, instability of the container/closure at — formulation temperature for a couple of minutes is unacceptable.

Question 6: Controls for delivered dose life stage means (presented in Section 6.2.5)

As evaluation of extensive delivered dose data obtained (release data on Phase 3 clinical batches and primary stability data generated so far) indicates that a significant proportion of tests for SYMBICORT pMDI will not meet the — label claim life stage means requirement recommended in the draft FDA guidance for NDIs and DPIs. The Phase 3 product specification did not contain the life stage mean requirement. AstraZeneca is considering several approaches to control delivered dose life stage means and would appreciate the Agency's comments on the acceptability of the use of 1 or more of the following approaches:

- *Define the target based on data provided in the NDA submission for each life stage and center the requirements around these (potentially different for each life stage) rather than around 100% label claim (LC).*
- *Evaluate beginning, middle and end life stage means against the overall mean of the sample to better control a potential through life trend.*
- *Allow different ranges centered around the corresponding target for the 3 life stages to take potential differences in dose variability for different life stages into account. Ranges will be based on the data provided in the NDA submission.*
- *Omit testing at the middle of canister, provided the middle life stage can be shown to be bracketed by beginning and end doses. If testing at the middle of canister is omitted, the AstraZeneca can increase the number of canisters tested at the beginning and end of canister life thus obtaining a more robust mean.*
- *Introduce a 2nd tier for life stage mean testing to obtain more robust means due to the larger sample size (the current FDA draft guidance delivered dose uniformity test does not allow entering 2nd tier testing if any life stage mean fails in the 1st tier).*

Targets and limits proposed will be based on data.

Does the Agency concur that the use of 1 or more of the above approaches is acceptable?

We note that the batches manufactured to this date do not utilize incremental propellant addition. It is likely that addition of propellant during filling will decrease the beginning to end of batch assay variability and decrease failures related to can-to-can variability.

If studies have demonstrated that any observed dosing trend is monotonic or linear in behavior, collection of DDU data at the beginning and end of container life will suffice.

If it is determined that the level of the middle determinations is outside the range formed by the levels of the beginning and end determinations, taking into account the suspension and the multiple drug substances characteristics of this formulation, it is inappropriate to assume behavior will be predictable in future batches based upon the limited data available from each presentation – each of which must be evaluated independently.

Behavior between these two extremes becomes a review issue and will depend on the can-to-can and batch-to-batch reproducibility demonstrated with each individual presentation.

Acceptance criterion for mean at each life stage should ~~be~~ of LC.

We note that in the displayed dose data, the formoterol component is consistently higher on average than the budesonide component in terms of percent of LC. Evidently one of the components appears to be filled above or below the LC target value. Ensure that manufacturing of the drug product is targeting the fill at 100% of LC. A significant portion of end-of-canister OOS results may be eliminated by targeting LC.

None of the other proposed approaches are acceptable.

Question 7: Aerodynamic particle size distribution (APSD) by Andersen impaction - choice of groupings (presented in Section 6.2.5)

AstraZeneca plans to propose a specification for aerodynamic particle size distribution based on 3 groupings:

- ***The amount less than _____ (fine particle dose; sum of _____ to filter) which characterizes the respirable portion of the dose.***
- ***The amount less than _____ (sub-micron dose; sum of _____ to filter) which characterizes the amount of the fine particle dose which could possibly be exhaled by the patient.***
- ***The total on impactor ('mass balance'; sum of throat, all stages and the filter). The combination of control over the total on impactor and the fine particle dose also allows indirect control over the non-respirable fraction of the dose.***

For the fine particle dose and sub-micron dose groupings, limits for the can mean will be proposed based on data. The total on impactor parameter will be controlled for each individual impactor run (see Question 8). If justified by data, the specification may be based on the beginning of can life only.

Does the Agency find this proposal to control aerodynamic particle size distribution based on 3 groupings acceptable?

This is a review issue. There should be adequate control to assure consistency of the APSD of future batches. Considering the difference in mass emitted per actuation between the formoterol and budesonide components, there may need to be two methods for evaluation of the PSD which take into account the differing number of actuations optimum for this analytical method.

The number of stages and combinations in these groupings are API-dependent. The individual stage data for each API must be evaluated independently to arrive at stage groupings for control purposes.

The assignment and number of stages in each group and the associated acceptance criteria will be made such that the complete particle size profile for each API is

controlled and the necessary discriminatory ability is present to detect shifts in the distribution that may be stability related.

Question 8: Aerodynamic particle size distribution by Andersen impaction - system suitability by control of mass balance (presented in Section 6.2.5)

The system suitability of the Andersen method will be addressed by controlling the mass balance of each individual impactor run. An approach based on the output from industry discussions with the Agency (PQRI Mass Balance Group) will be proposed in the NDA submission. Possible elements of this include:

- *Target level for the mass balance may be chosen in the range label claim to account for net systematic bias such as stage losses or other methodological bias.*
- *Different targets may be used for beginning and end measurements to take a possible through life trend into account.*
- *If a test fails, retesting will be performed using a new can as the original can cannot be retested for the specified actuation numbers, and in many cases the retest would have to be carried out beyond the label claim number of actuations.*
- *Only 1 retest per system suitability failure is allowed, otherwise an out of specification investigation will be performed.*

Targets and limits proposed will be based on data.

Control of the mass balance for each individual impactor run as part of the specification will ensure that repeated failure due to sub-normal quality product will result in failure of the batch.

Does the Agency find this approach to control the system suitability of the Andersen method acceptable in principle?

No. The total mass of drug emitted for both APIs and collected on all stages and accessories per determination should be between percent of label claim on a per actuation basis. Separate targets for beginning- and end-of-canister testing are inappropriate.

Mass balance data should be presented in terms of the percentage of the total mass found on the various stages and accessories relative to the label claim. No adjustment of the target for mass balance will be accepted. We note that the global mean mass balance results in Tables 3 and 5 (Attachment 1) show an overall mass balance of of Label Claim. The formoterol data in Tables C3 and C4 in Attachment 1 show very similar behavior. These global means provides evidence that no net systematic bias exists and thus no change in target for mass balance can be justified.

Justification for a second tier of testing must be provided and will be evaluated in light of all associated emitted dose and cascade impaction data.

The use of mass balance is for drug product release testing, not just system suitability validation.

Question 9: Colors used to differentiate _____ product strengths (presented in Section 6.2.6.1)

Does the Agency agree that the choice of colors used to differentiate _____ product strengths is adequate?

Question 10: Shield actuator and _____ launch strategy (presented in Section 6.2.6.1)

Does the Agency concur with AstraZeneca's proposal to launch with the shield actuator _____ ?

We have no concerns at this time. _____
at _____

Question 11: Mechanical testing for the shield actuator _____ (presented in Section 6.2.6.1)

Does the Agency concur with the mechanical testing proposed for the shield actuator _____ and is the planned testing sufficient?

We have no concerns at this time.

Question 12: Format for provision of drug product stability data (presented in Section 6.2.7)

Due to the large amount of stability data that will be generated for the NDA submission, AstraZeneca will provide quantitative data for each stability batch and time point as means and ranges in '3.2.P.8 Stability'. All individual quantitative data will additionally be provided electronically, eg, as either EXCEL (.xls) or SAS transport files (.xpt). Does the Agency concur with this proposal?

No. All individual data should be submitted in the NDA. Submit electronic data as SAS transport files (.xpt). The individual detailed data sets may be submitted in a separate volume(s) from the summary data with appropriate cross-references.

Additional Comments:

1. We note that in section 3.2.13 you omit quantitation and identification of particulates greater than [redacted]. We expect all foreign particulates to be quantitated and identified.
2. In section 3.2.28, you state "*AstraZeneca has interpreted this comment from the End of Phase 2 meeting to mean that evaluation of impurity levels is required rather than full performance testing for critical batches.*" This is an incorrect interpretation. Critical batches must be tested for both impurity levels, all performance parameters, and all other relevant parameters during the period they are administered to patients. If the critical batches are also primary stability batches, then the performance parameters are determined at the time points bracketing the clinical trial start and end dates.
3. All acceptance criteria (container closure and drug product at release and stability) proposed in the NDA must be reflective of current manufacturing capabilities. Provide detailed data to support all proposed acceptance criteria. No comments on acceptance criteria will be provided by this Division at this time since the data supporting any proposal must be reviewed.
4. In regards to Dose Proportionality (3.2.39):
 - a. Dose Content Uniformity: We note that the data in Table 2 (p. 137) show batches P6037 and P6039 have high mean doses of formoterol at the end of canister (1 [redacted] of LC). Also, the mean formoterol dose overall is [redacted] at the end of canister for all strengths.

This may indicate a trend in end-of-canister dose that requires additional evaluation of formulation stability over the life of the canister. This trend is not seen in either beginning- or middle-of-canister test points. Review of the detailed data will be necessary for better understanding of the characteristics of this potential problem.
 - b. Particle Size Distribution (PSD): The product must be tested using the current methods for measurement of PSD and mass balance before the individual determination data can be reviewed and the dose proportionality with respect to PSD can be evaluated.
5. Comparison of PSD
 - a. Oxis Turbuhaler M2 comparative PSD data are inadequate. The [redacted] under uncontrolled airflow conditions does not adequately characterize the particle size distribution.

- b. Characterization of the PSD of this batch of drug product for comparative purposes should be accomplished in an Andersen CI using a fixed volume of air (4L) at 28.3 L/min, as is customary for dry powder inhalers. Uncontrolled air flow does not sufficiently mimic patient inhalation characteristics – particularly those with compromised lung function.
 - c. Individual stage data from both the M2 device and the budesonide pMDI are necessary for comparative purposes. Mean data alone are inadequate for this purpose.
6. Comparison of Dose Content Uniformity
- a. Oxis Turbuhaler M2 comparative DCU data are inadequate. The dose uniformity determination should be accomplished at a fixed volume of air through the device ~~and~~ and with range of flow rates ~~and~~.
 - b. Comparative data for DCU must include both M2 device (under the above constraints) and budesonide pMDI individual dose data to provide an indication of the dose-to-dose variability for both comparator drug products.
7. Manufacturing
- a. Conditioning time (6.1.4.3) of micronized formoterol fumarate must be validated with evaluation of the effect of conditioning time and humidity on amorphous content and particle size distribution. See comment 6 from the EOP2 meeting minutes.
 - b. Drug substance overage and propellant addition rate for Symbicort manufacturing must be justified by data. For this purpose, submit a profile of assay determinations throughout the manufacturing run particularly around the points in the manufacturing run when additions of propellant occur.
 - c. A two-week lagging period is inadequate. At least a three-week period is generally required.
8. Specifications
- a. Institute a specific assay for fumarate in the specifications for formoterol fumarate dihydrate.
 - b. Absence ~~of~~ organisms must be established in every batch of formoterol fumarate dihydrate micronized, along with acceptance criteria for molds and yeasts.

9. Drug Product Specification

a. Include the following parameters.

- Specific ID test for fumarate ion
- Valve delivery (_____ for mean, _____ for individuals)

b. Acceptance criterion for *Individual unspecified related substances* must be _____.

c. Mass balance acceptance criterion should be _____ LC.

d. Stage groupings for cascade impactor testing will be set once the individual stage data are reviewed.

e. The quantity of foreign particles should be controlled in the ranges of _____.

f. As per comment 15 in the EOP2 meeting minutes, "include inspection of canister walls...for deposited drug". Therefore, modify the Appearance test method so as to preclude deposition on the internal canister wall (e.g., chill and pour off) so that unusual deposition may be evaluated.

10. You have provided a diagram of a _____ valve in Figure 6. This valve is atypical of _____ valve design and can not be used as justification for selecting the _____ valve. _____ are always used as secondary, not primary canister seals.

If there are any questions, please contact Colette Jackson, Regulatory Health Project Manager, at 301-827-9388.

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Drafted: October 28, 2004
Initialed: Barnes/ October 28, 2004
 Rogers/ October 28, 2004
 Lostritto/ October 28, 2004
 Chowdhury/ October 29, 2004

Finalized: October 29, 2004

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HFD570/Div. Files
HFD-570/Meeting Minutes files
HFD-570/Jackson
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HFD-570/Lostritto
HFD-570/Rogers
HFD-570/Gunkel
HFD-570/Starke
HFD-570/Robison
HFD-570/Sun
HFD-570/Duffy

Drafted by: CCJ/NOVEMBER 8, 2004

Initialed by:

Rogers/December 16, 2004
Lostritto/ December 16, 2004
Starke/November 26, 2004
Robison/November 24, 2004
Sun/ November 24, 2004
Chowdhury/January 3, 2005

final: CCJ/JANUARY 5, 2005

MEETING MINUTES

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/s/

Sandra Barnes
10/29/04 10:07:40 AM
CSO

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/s/

Colette Jackson
1/5/05 01:42:59 PM

9/14/04

IND 63,394
Symbicort pMDI

We have completed our Clinical review of your submission to IND 63, 394 dated August 11, 2004. We have the following comment:

This is to make a correction in the minutes of the pre-NDA meeting held on June 28, 2004, between members of the Division of Pulmonary & Allergy Drug Products and representatives of AstraZeneca regarding Symbicort pMDI for long-term maintenance treatment of asthma.

Page 18 of the minutes, first paragraph, contains the statement, "...the two co-primary endpoints for both of the pivotal studies (Study 716 and 717) were changed after the studies had started." This is in error. The change that occurred was as follows: One of the original co-primary endpoints, withdrawals due to pre-defined asthma events, was relegated to a secondary endpoint. One of the original secondary endpoints, pre-dose FEV1, was elevated to co-primary endpoint. The original complementary co-primary endpoint, post-dose FEV1, never changed.

If there are any questions, please contact Ms. Colette Jackson, Project Manager, at 301-827-9388.

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cc:

HFD-570/Division Files
HFD-570/Gunkel
HFD-570/Starke

Drafted: CCJ/September 9, 2004

Initialed: Barnes/September 13, 2004

Gunkel/September 14, 2004

Starke/ September 14, 2004

Chowdhury/ September 14, 2004

Finalized: CCJ/September 14, 2004

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Colette Jackson
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CSO

MEETING MINUTES

DATE: June 28, 2004
TIME: 1:00 PM - 2:30 PM
LOCATION: Parklawn Conference C
APPLICATION: Pre-NDA meeting IND 63,394
DRUG NAME: Symbicort (budesonide/formoterol) pressurized MDI (pMDI)
INDICATION: Long term maintenance treatment of asthma
IMTS#: _____

AstraZeneca (AZ)

Jane Chang, Director, Preclinical Sciences, Safety Assessment
Mark Desiato, Director, Regulatory Affairs
Mike Gillen, R.Ph., Director, Clinical Pharmacology, Experimental Medicine
Laura E. Garcia-Davenport, M.S., Associate Director, Regulatory Affairs
William Mezzanotte, M.D., Executive Director, Clinical Research
Christopher Miller, Director, Biostatistics Project Team
Chris O'Brien, Director, Clinical Research
Liza O'Dowd, Sr. Director, Clinical Research
Barry Sickels, M.S., Executive Director, Regulatory Affairs
Douglas Smith, Executive Director, Development
Ray Stanley, Sr. Manager Statistical Programming
Piat Vervaet, M.D., Sr. Medical Director, Drug Safety

FDA, Division of Pulmonary & Allergy Drug Products (unless otherwise noted)

Timothy Robison, Ph.D., Pharmacologist
Joseph Sun, Ph.D., Supervisory Pharmacologist
Sandra Suarez-Sharp, Ph.D., Clinical Pharmacology & Biopharmaceutics (CPB) Reviewer
Emmanuel Fadiran, Ph.D., CPB Team Leader
Harry Gunkel, M.D., Medical Reviewer
Peter Starke, M.D., Medical Team Leader
Badrul Chowdhury, M.D., Ph.D., Director
Christine Yu, R.Ph., Regulatory Project Manager

Don Collier, Regulatory Technology Specialist, Office of Information Management
Steve Wilson, Ph.D., Deputy Director, Division of Biometrics II

Background

AstraZeneca (AZ) requested a pre-NDA meeting to discuss the content and format of the NDA for Symbicort pMDI for long term, maintenance treatment of asthma in adults _____

_____ AZ plans to submit the NDA during second quarter 2005. Briefing packages for the meeting were received May 6, 2004.

Agenda

Pharmacology & Toxicology
Clinical Pharmacology & Biopharmaceutics (CPB)
Clinical
Regulatory
Electronic submission format

Guidances for Industry referenced during the meeting

Guidances represent the Food and Drug Administration's (FDA's) current thinking on a topic. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

Minutes

The following slides presented by the Division include AZ's questions from the briefing package, followed by the Division's responses. Additional discussions during the meeting are captured between the slides.

Pharmacology & Toxicology

NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

5-1. Does the Agency agree that the completed preclinical pharmacology/toxicology studies with budesonide/formoterol combination in addition to toxicology documentation for both mono-products support the registration of Symbicort pMDI?

RESPONSE: Pending final review of studies, we concur. Issues regarding impurities, degradants, extractables, and leachables should be adequately addressed as communicated in past meetings.

5-2. Does the Agency agree that toxicology data derived from excipients used in the completed long-term studies with another AstraZeneca compound (formerly being developed as a pMDI formulation) in rats and dogs support the registration of SYMBICORT pMDI?

RESPONSE: Pending final review of studies, we concur.

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5-3. Does the Agency agree with the proposed content /format for the preclinical data as outlined in Section 5 of this briefing document?

RESPONSE: We concur with the proposed content/format. Our review will be principally focused on studies with the budesonide/formoterol combination and formoterol alone. For budesonide, cross-referencing to studies in NDAs is acceptable.

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Upon AZ's inquiry, the Division responded that no further studies are needed.

Clinical Pharmacology & Biopharmaceutics (CPB)**Clinical Pharmacology Questions****Question 6.1**

Pharmacokinetic and pharmacodynamic data for budesonide are currently included in the approved package insert for PULMICORT TBH, much of which is not directly related to the inhalation delivery device (i.e., ADME, oral absorption, drug-drug interaction, protection against allergen challenge, etc.). It is proposed that appropriate information (device independent) will also be included in the package insert for SYMBICORT pMDI through text cross-referencing to the PULMICORT TBH package insert. It is not planned to include study reports that support these statements nor summarize these studies within the SYMBICORT NDA, as the supporting data in NDA 20-441 for PULMICORT TBH will be referenced.

Does the Agency agree that this is an acceptable approach?

Answer

- Yes, we agree

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Clinical Pharmacology Questions, cont.**Question 6.2:**

Pharmacokinetic and pharmacodynamic data for formoterol were generated to support the OXIS TBH development program (IND 44,271) although an NDA has not been submitted for this product in the United States. Some of these data are not directly related to the inhalation delivery device (i.e., ADME, protein binding, etc.). However, they are useful in describing the basic pharmacokinetic properties of formoterol in the package insert. The complete study reports for these studies will be included within the SYMBICORT NDA and the studies will also be briefly summarized in Module 23.2 (Summary of Clinical Pharmacology Studies)

Does the Agency agree that this is an acceptable approach?

Answer

- Yes, we agree

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Clinical Pharmacology Questions, cont.

Question 6.3:

Data sets will be provided to the Biopharmaceutics reviewer for the core group of six PK studies performed with SYMBICORT pMDI (SD-039-0721, -0722, -0723, -0724, D5896C00010, D5896C000111). For each study, the data sets will be provided in ASCII format - one file for bioanalytical data and one for the PK parameters, along with a readme.txt file, which defines the data sets.

- Does the Agency have any specific technical requests regarding the format for submission of PK data sets?

Answer

- Submit individual PK data for every study as SAS TRANSPORT files.

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Question 6.3, cont...

Does the Agency agree with the AstraZeneca proposal to provide data sets for the six core PK studies submitted in the NDA?

Answer

Also provide data from the following studies:

- Individual PK data from asthmatic children 6 years and older (data from phase III studies)

- Individual PK data for study SD-039-0713: study of the relative BA of symbicort pMDI vs. Oxis TBH plus pulmicort TBH.

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Question 6.3, cont...

- *We highly recommend that you conduct a population PK analysis on the budesonide/formoterol pharmacokinetic data. This analysis will be useful to define not only the effects of age (children vs. adults) on the PK of the drugs, but also the effects of formulation/devices (Symbicort pMDI vs. Symbicort TBH, vs. Pulmicort TBH vs. Oxis TBH etc), QD vs. BID dosing, healthy versus asthmatics, gender differences, etc., on the PK of budesonide and formoterol.*

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Clinical & Regulatory

4-1. Does the Agency agree with the format and proposed content of the highlighted key sections in the draft prescribing information?

- Adhere to 21 CFR 201.57 for format and content. The brief draft format provided appears to be acceptable.
- Study 726 appropriately belongs with the other placebo-controlled studies in the draft Adverse Event table.
- There will be additional comments about content following the responses to the other questions.

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AZ stated that study 726 was omitted because it differed somewhat in design by including a Symbicort run-in period. The Division acknowledged the difference but re-stated its preference that all the placebo-controlled studies be represented in the Table. The Adverse Events included in the Table for Study 726, however, should not include those that occurred during the run-in period.

7-1. Does the Agency agree that the results of Study SD-039-0729...support the use of OXIS TBH...as an appropriate monotherapy comparator to SYMBICORT pMDI in the Phase 3 development program?

- Oxis TBH appears to be an acceptable mono-product comparator based on the information provided to the Division to date.

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AZ further queried whether the Division can state categorically that results of Study SD-039-0729 are acceptable. The Division stated that it cannot make that statement at the present time because the entire study and its context within the NDA have not been reviewed yet. The Division has reviewed the information provided about the study to date and has stated that the study appears to have met its objectives. A complete review of the NDA would be needed for final determination.

7-2. AstraZeneca does not intend to conduct a growth study with SYMBICORT pMDI. As included in the IND and End-of-Phase 2 briefing package, in lieu of performing a growth study, AZ proposes to establish a link to existing growth data for PULMICORT TBH. In accordance with the November 2001 FDA draft guidance "Evaluation of the effects of orally inhaled and intranasal corticosteroids on growth in children", a pharmacokinetic study in pediatric (6-11 years old) subjects with asthma will be performed to establish a bridge between SYMBICORT pMDI and PULMICORT TBH. Does the Agency agree?

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- Growth data for Symbicort pMDI or an orally inhaled budesonide that meet current standards will be needed. If those data are available, submit them with the NDA. If the data are for a budesonide product, there will need to be a PK link to Symbicort pMDI.
- If data are not available, a growth study will need to be performed.

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AZ asked whether the existing Pulmicort data were sufficient to allow for use in the Symbicort label.

The Division noted that the information about growth submitted in the Pulmicort NDA was from literature reports only and expressed reluctance about relying on data from several years ago to support the NDA for Symbicort. The standards for study designs as well as understanding of the effects of steroids on growth have advanced in recent years. Upon Division' inquiry, AZ stated that they do not have ownership of the published studies and had not sponsored the studies.

Regarding AZ's inquiry about using growth data from Rhinocort Aqua (budesonide) Nasal Spray studies, the Division reiterated that data from studies using an *orally inhaled budesonide* (not a nasal spray) product would be needed. Although absence of a growth study probably would not affect approval of the NDA (a post-marketing commitment might be satisfactory), the Division encouraged AZ to generate the necessary data. It is AZ's option to decide whether that study would be with Symbicort or with budesonide with a PK link to Symbicort.

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7-3. Does the Agency agree with the pooling strategy for the integration of safety data from the SYMBICORT pMDI studies?

- The proposed pooling strategy is acceptable. Pooled safety analyses should also conform to pooled results presented in the labeling. For example, the groupings of Adverse Events in the draft package insert (pediatrics, long-term safety) should be supported by pooled analyses in the NDA.

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7-4. Historical data supporting the safety and efficacy of budesonide will be provided by cross-reference to the information on file in PULMICORT TBH NDA 20-441, PULMICORT RESPULES NDA 20-929 and RHINOCORT AQUA NDA 20-746. Does the Agency agree?

- Yes

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7-5a. Does the Agency agree with the strategy of classifying the OXIS TBH and SYMBICORT TBH clinical studies into categories (1 through 8) based on study design and relevance to the SYMBICORT pMDI safety summary?

- The categorization scheme is acceptable.

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7-5b. Does the Agency agree with AstraZeneca providing differential amounts of safety information regarding these legacy studies as outlined?

- The plan is acceptable. However, it is not necessary to submit Clinical Study Reports for OXIS TBH and Symbicort TBH studies.

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AZ stated that they will, however, submit the information from the above studies needed for Clinical Pharmacology & Biopharmaceutics.

7-6. Safety information regarding SYMBICORT pMDI will be provided at the time of the 4-month safety update in accordance with 21 CFR 314.50(d)(5)(vi)(b). No information concerning OXIS TBH and SYMBICORT TBH will be included; for these products, safety information will continue to be provided as required by 21 CFR 312.32 (IND Safety Reports) and 21 CFR 312.33 (Annual Reports). Does the Agency agree?

➤ Yes

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7-7. Adverse events for the SYMBICORT pMDI studies to be included in the NDA will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). However, adverse events in the OXIS TBH and SYMBICORT TBH Clinical Study Reports have been coded using the Astra Adverse Event Dictionary (AAED)...AstraZeneca has recoded the adverse events in the OXIS TBH and SYMBICORT TBH ISS documents using MedDRA version 6.0. This will result in adverse events being presented...with slightly different terminology than presented in the original Clinical Study Reports...this approach will provide the Agency with the capability to make the most direct comparison with the SYMBICORT pMDI adverse event data, as the NDA Summary of Clinical Safety will be coded using MedDRA version 7.0. Does the Agency agree with this approach?

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- Since the recoding has already occurred, submit both versions. Include original codings for the adverse events in the OXIS TBH and Symbicort TBH studies.

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AZ stated that providing both versions of the coding for all adverse events may be difficult and demand much of their resources. Therefore, AZ would prefer to provide a “map” for the new coding of terms so that adverse events can be compared across the studies and products in the NDA.

The Division expressed appreciation for AZ's efforts to facilitate review and the work already done on recoding, but also expressed concern about adding another layer of interpretation to the events reported by investigators. After some discussion about how recoding might affect some adverse events, especially those of the respiratory system, AZ agreed to submit examples of how term changes would be mapped for Division review before submitting the NDA. If original terms are to be used in OXIS and Symbicort TBH studies, AZ would prefer to submit full study reports of the core studies with those products, rather than omit them as was discussed under Question 7-5b above.

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7-8. With the exception of two Phase 1 studies that include subjects with COPD, AstraZeneca will not include data in the NDA from any ongoing (or newly planned) studies in subjects with COPD, since these studies are evaluating a different patient population than those conducted in subjects with asthma, and are not believed to be relevant for inclusion in the NDA for Symbicort pMDI. Does the Agency agree?

- No. Refer to 21 CFR 314.50(d)(5)(iv): the clinical data section should include “any other data or information relevant to an evaluation of the safety and effectiveness of the drug product...including information derived from clinical investigations...of uses of the drug other than those proposed in the application...”

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7-9. In an effort to comply with the Agency's guidance “Integration of dose counting mechanisms into MDI drug products” regarding a dose counter, and to meet the needs of the asthma patients and caregivers by providing the US market with an optimal combination therapy as quickly as possible, AstraZeneca proposes the following:

- The CMC information relevant to the actuation counter will be provided in the NDA
 - The final results of the patient use study will be provided during the Agency's review of the NDA.
- Does the Agency agree with AstraZeneca's proposal?

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➤ The NDA should be complete and able to support the intended product at the time of submission. Submitting results of new studies during the review cycle is discouraged, and review of the study might not be completed during that review cycle.

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AZ explained that although several issues had delayed readiness of the actuation counter, they would like to include CMC data with the NDA submission without the patient use study. The dose counter would not be ready for clinical trials until January 2005; therefore, the patient use study would not be conducted in time for the NDA submission planned for second quarter 2005.

The Division recommended that AZ either delay NDA submission until the clinical study results are available or submit a post-approval supplement.

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8-1. AstraZeneca proposes that the Risk Management approach for SYMBICORT pMDI would consist of professional product labeling, patient use instructions, and robust pharmacovigilance. Does the Agency agree with AstraZeneca's approach for the Postmarketing Risk Management of SYMBICORT pMDI?

➤ Yes

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8-2. Does the Agency agree to issue a Pediatric Written Request for SYMBICORT pMDI?

➤ At the present time, the Division does not perceive any public health imperative that supports issuing a Pediatric Written Request for Symbicort pMDI.

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The Division noted that because Symbicort pMDI is a fixed-dose combination product, and the dose cannot be titrated, it is not suitable for young children.

8-3. Financial Disclosure Information will only be provided for the Phase 2 and Phase 3 SYMBICORT pMDI studies. AZ believes that these studies constitute the "covered studies". Does the Agency agree?

- Yes

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10-1. AstraZeneca believes it would be important to establish an interaction plan for the NDA review. A detailed interaction plan is proposed. Does the Agency agree with the proposed plan?

- The Division intends to maintain its customary close interaction with the applicant during the review of the Symbicort pMDI NDA. A special interaction plan is not necessary.

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Additional Comments

- The Symbicort pMDI clinical program is complex with different endpoints in varying populations. The complexity is amplified by a combination product in — different doses, twice-daily — dosing programs, and pharmaceuticals issues with the different comparators. It will be important that the data in the NDA be presented in a cogent manner to organize and address these many elements in a way that persuasively supports the intended indication and claims.

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Additional Comments

- To detect potential outlier effects, in addition to central tendency analyses, perform categorical analyses of pertinent data (e.g., vital signs, labs, ECG's) and present the results in the form of shift tables.

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Example: Safety Shift Table

Treatment	Baseline	Final				
		Maximum Post-Baseline ALT				
		Low	Normal	>ULN	>3-5xULN	Missing
Active	Low	6	22	4	2	1
	Normal	0	155	7	3	2
	>ULN	0	2	5	3	1
	Total	6	179	16	8	4
Placebo	Low	4	20	0	0	1
	Normal	3	185	3	1	3
	>ULN	0	0	1	0	0
	Total	7	205	4	1	4

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Towards the end of clinical discussions, AZ pointed out that, as described on page 62 of the briefing package, the two co-primary endpoints for both of the pivotal studies (Study 716 and 717) were changed after the studies had started. Because this change had already been made and the studies completed, AZ had not included this issue as a question to be discussed at this Pre-NDA meeting. However, AZ requested Division confirmation that this change would not affect review of the NDA.

The Division responded that this issue, which affects the two pivotal studies for the NDA, should have been addressed as a meeting question rather than brought up during discussions. The Division stated that this will be a review issue. AZ must include a strong justification for changing the primary endpoint for the pivotal studies with submission of the NDA. Additionally, because the primary endpoint was changed after the studies had started, the NDA must also include a detailed description of the timing of events, particularly regarding data that were collected before and after the changes. AZ must clarify and justify that the change in co-primary endpoint did not affect how investigators behaved or how individual patients were treated during the studies. It may also be appropriate to analyze results before the change separately from those after the change, in addition to overall. The Division requested that AZ submit pdf and ASCII programs for the primary analysis, workfiles analyzed, and the actual statistical models used for the studies, so that the Division would be able to thoroughly review AZ's submitted analyses.

AZ noted that that they currently did not have any data in house.

Electronic submissions

9.1 Does the Agency agree with the proposed format of the eNDA submission for SYMBICORT pMDI described in Appendix C?

- The proposed format, eNDA with a CTD "read" is quite acceptable.
- There are some minor "numbering" corrections as I've noted in the handout and the handout will be included in the minutes of this meeting.

Continued on next slide

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See Attachment to minutes, "Sample TOC Corrections Based on eCTD standards."

9.1 Does the Agency agree with the proposed format of the eNDA submission for SYMBICORT pMDI described in Appendix C?

Continued from previous slide

- Do not create "extra" headings / groupings that are not listed in the ICH documentation
 - ◆ Subunits to the CTD standard numbering and nomenclature can be created
 - ◆ These "navigational" subunits *should not be shown in the TOC*
 - ◆ These "navigational" subunits can be **tabbed** in paper versions or shown in the subunit text as an additional TOC, i.e., in your example in appendix C, 2.3 QOS could have a "text preamble" that would be a TOC listing the 2.3.S, 2.3.P, etc., sections.
- Extract from the eCTD documentation for XML coding the numbering and nomenclature, these are the "latest" iterations of the CTD format and are, naturally, "backward" applicable to the entire CTD structure, paper and electronic
- These documents can be found at:
 - <http://www.fda.gov/cder/regulatory/ersr/ectd.htm>

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9.2 In lieu of including Synopses of Clinical Study Reports in Module 2.7, hypertext links will be used to access the Synopses in Module 5.

Does the Agency agree?

Alternatively, if hypertext links are not accepted, AZ requests a "waiver" for exceeding the page limits for the Clinical Summary, identified in the CTD guidance by approximately 150 pages. Will the agency grant this "waiver"?

- You may use hypertext links to these synopses
- Be careful that you do not fall into a common problem of including too much "supporting" data in Module 2

Continued on next slide

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

9.2 In lieu of including Synopses of Clinical Study Reports in Module 2.7, hypertext links will be used to access the Synopses in Module 5.

Does the Agency agree?

Continued from previous slide

- Notes on your 9.1 from page 84 of package:
 - ◆ Pay particular attention to content of Module 2
 - Per Guidance, the content in Module 2 should be short and concise... "Narrative descriptions should be brief (similar to an abstract for a journal article)..."
 - Include "summaries" only, if supporting data is needed, make "reference" to it and provide hyperlinks to its location as opposed to including it "for ease" of use in Module 2

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Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

9.2 In lieu of including Synopses of Clinical Study Reports in Module 2.7, hypertext links will be used to access the Synopses in Module 5.

Does the Agency agree?

Continued from previous slide

- ◆ Refer to the newer Guidances for the eCTD with regards to “content” and linking procedures
 - Newer Guidances suggest “abridged” study synopses in Module 2 with links to the “full” version(s) contained in Module 5
 - If after “trimming” as much as possible you still find your application “over limit” on the specs, the “overage” you are describing won’t be a RTF issue.

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

9.3 AZ does not plan to generate patient profiles for inclusion in the SYMBICORT pMDI NDA. Rather, at the Division’s request, specific patient profiles will be provided as needed during the NDA review.

Does the Agency agree?

- This is per Guidance and quite acceptable
- We have the tools to build Patient Profiles from “raw” data supplied to Module 5
- We appreciate your willingness to provide these for us “on demand” and any specific requests will be addressed by the Medical Officer if and when needed

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

9-4 Does the Agency agree that individual subject datasets (CRF tabulations) in the format of SAS Transport Files will only be need to be provided for the Phase 2 / 3 SYMBICORT pMDI studies?

- SAS Transport files (.xpt) format for datasets are the current standard for archival.
- SAS Transport files are easily manipulated into the various formats used by the Agency
- ASCII format for data is *not* a preferred archival format and is used in special instances where source programming for analysis is needed.
- Scope of the data provided is a Review Discipline issue and will be covered by the appropriate discipline

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

9-5 It is anticipated that several datasets in the SYMBICORT pMDI NDA will be close to / or 100 MB in size. AstraZeneca believe the size of these datasets will be acceptable to the Agency based on the ICH's decision to increase the file size limit to 100 MB. AstraZeneca expects that the Agency will have incorporated the ICH recommendations at the time of the NDA submission.

Does the Agency agree that datasets of this size (~100 MB) are acceptable for the NDA submission?

- Yes

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

In response to AZ, Mr. Don Collier stated that 90 - 105 MB would be acceptable. However, for files that are bigger, AZ should create smaller files using logical breaks in the datasets.

The meeting was adjourned at this time.

SYMBICORT@(budeonide/formoterol)pMI
pre-NDA Briefing Document
Appendix C Draft NDA table of Contents

		Archive Copy Location (folder\file name)
Module 1: Administrative and Prescribing Information		
1.2	Cover Letter	n12345\cover.pdf
1.1.2	FDA Form 356h	n 12345\356h.pdf
	*Not used in CTD Format	n12345\ndatoc.pdf
1.3	Administrative Documents	other\patinf.pdf
1.3.5.1	Patent Information ^a	other\patinf.pdf
1.3.5.2	Patent Certification ^a	other\patcert.pdf
1.3.3.	Debarment Certification ^a	other\debar.pdf
	Establishment Description ^a	NA
1.3.2	Field Copy Certification	other\fieldcer.pdf
1.1.3	Copy of User Fee Cover Sheet (FDA form 3397)	other\userfee.pdf
1.3.4	Financial Disclosure Information ^a	other\finandis.pdf
1.4.1	Letter of Authorization	other\ltrauth.pdf
1.9.2	Waiver Request ^o	other\pedwaiv.pdf
1.12.14	Environmental Assessment	cmclenviron.pdf
1.9.6	Statements of Claimed Exclusivity and Associated Certifications	other\exclusivity.pdf
1.4.4	List of INDs and NDAs	clinstat\indsndas.pdf
1.13.10	Foreign Marketing History	summary\foreignm.pdf
	Not a valid CTD Heading	Other\
1.16	Risk Management Program	other\riskman.pdf
1.14	Labeling	

		Archive Copy Location <i>(folder/file name)</i>
1.14.1.5	Labeling History	labeling\history.pdf
1.14.1.3	Proposed PPI	labeling\proposed.pdf
	Currently Used Labeling Text	NA
	Last Approved Labeling Text	NA
	Final Printed Package Insert	NA
1.14.1.1	Carton label (Draft)	
1.14.1.1	Container Label (Draft)	
1.14.3.2	Other Labels ? Approved Labeling for listed drugs?	
1.14.3.3	References ? Labeling text for reference listed drugs?	
1.14.1.2	Annotated Labeling Text	summary\annotated.pdf
	Module 2: Common Technical Document Summaries	summary\sumtoc.pdf
	Module 3: Quality	cmc\cmctoc.pdf
	Module 4: Nonclinical Study Reports	pharmtox\pharmtoc.pdf
	Module 5: Clinical Study Reports	clinstat\clintoc.pdf

^a Submitted both as paper (wet-ink) and electronic.
 NA not applicable

* This file (the NDA TOC) if included, can either be part of the cover letter or an individual file with no CTD association and put in the root folder as described. It is not, however, a valid listing in the CTD and as such has no number assignable to it.

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 Deliberative Process

Withheld Track Number: Administrative-

of the 95% CI for a difference is set at 0 s. Support for this distinction should be provided. Such support may come from comparisons within the same study arms of 1 puff, 2 puffs, and 4 puffs of Formoterol TBH or Symbicort.

- The proposed washout period for this study of 2 to 10 days is inappropriate for a drug with a prolonged half-life like formoterol. A washout period minimum of 3 days is recommended.
- Trial 729 should include pharmacokinetic measurements to (hopefully) validate the previous results in healthy subjects that suggest that formoterol in Symbicort is, if anything, less systemically bioavailable than the formoterol in Oxis TBH. This PK aspect of the trial will be also considered relevant in judging the ultimate results of the pharmacodynamic comparability of the two products.

In addition, the Division conveyed the following comment multiple times regarding the Symbicort asthma program:

We highly recommend that at least one of the proposed phase 3 trials (716, 717, or 718) should include a treatment arm of formoterol OXIS TBH with Budesonide pMDI taken together as individual ingredients. Such a treatment arm provides invaluable perspective on addressing the concerns about pharmaceutical differences between Symbicort and the individual treatment arms.

The Division concluded that the pharmaceutical results from protocol 729 are pivotal to Symbicort's phase 3 asthma studies, the phase 3 studies, and the phase 3 once-daily Symbicort programs. AstraZeneca acknowledges the risk that has been taken with conducting their pivotal protocol 729 parallel to other studies and noted that parallel studies are conducted in order to meet their timelines. AstraZeneca also confirmed that the Division's advice about adding a separate treatment arm of formoterol OXIS TBH with Budesonide MDI taken together but separately had been taken. Prior to studies with subjects, AstraZeneca plans to send in the results of protocol 729 to the Division for comments and possible further discussion. AstraZeneca anticipated that this would likely occur in the 3rd quarter of 2003. AstraZeneca would like to send in a short synopsis of their protocol for comments by the Division prior to sending the final protocol. The Division noted that protocol concept sheets and multiple iterations of protocol designs are typically reserved for unique indications or priority drugs that provide a public health benefit that is currently unmet. Under PDUFA3, one such application per Division may be designated for priority review, and communications in such situations (including protocol concept sheets that are then developed into final protocols) would be frequent and collaborative between FDA and the sponsor. With current staffing, however, it is not possible for FDA staff to provide this level of commitment for every submitted protocol. The Division commented that even the meeting being held at present with AstraZeneca is unusual in nature, and that such meetings are not typically granted with every sponsor. The Division therefore suggested that AstraZeneca submit their final protocol with specific questions outlining areas of concern.

In regards to the CAC assessment of formoterol studies, there was an Executive CAC meeting April 14, 1998 to discuss mouse/rat carcinogenicity studies conducted with formoterol. Both studies were considered acceptable based on plasma exposure between animals and humans and no evidence of genotoxicity for the drug; the respective plasma AUCs in mice and rats were 65 and 50 times human AUC at the highest dose tested. Thus, the mouse and rat carcinogenicity studies have been judged to be acceptable by the Executive CAC.

Minutes Preparer

Colette Jackson, Project Manager

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cc:

**HFD-570/Mann
HFD-570/Chowdhury**

Drafted: April 13, 2003

**Initialed: Mann/April 14, 2003
Chowdhury/April 14, 2003**

Finalized: CCJ/April 16, 2003

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this page is the manifestation of the electronic signature.**

/s/

Colette Jackson
4/16/03 11:44:47 AM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 4, 2002
TIME: 9:00 AM
LOCATION: Parklawn, Conference Room B
APPLICATION: Symbicort™ (budesonide/formoterol) pMDI

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION**Representatives of FDA**

Raymond Anthracite, M.D., Medical Officer
Marianne Mann, M.D., Deputy Division Director
Guirag Poochikian, Ph.D., Chemistry Team Leader
Brian Rogers, Ph.D., Chemist
Anthony Zeccola, Regulatory Management Officer

Representatives of AstraZeneca

Nola Bowles, BSc., Associate Director, Analytical Development
Ann Brindley, Ph.D., Associated Director, Analytical Development
Eric Couture, Ph.D., Director, Regulatory Affairs
Michael Gillen, Director, Clinical Pharmacology
William Mezzanotte, M.D., Director, Clinical Research
Andy Rignall, Ph.D., Manager, Analytical Development
Liuda Shtohryn, Pharm.D., Associate Director, Technical Regulatory Affairs
James Sullivan, Manager, Regulatory Affairs
Rob Whyard, BSc., Associate Director, Pharmaceutical Project Management

BACKGROUND: This meeting was held in response to a January 16, 2002 End of Phase 2 Meeting Request. Based on the number of questions that were included the Sponsor requested two meetings, one for CMC related questions and the other to include preclinical and clinical questions.

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Responses to Comments for 4/4/02 AstraZeneca Meeting for Symbicort MDI

1. AstraZeneca proposes that the testing detailed for povidone K25 and PEG 1000 provides adequate control for these materials. Does the Agency concur with this proposal?

Response

In addition to the compendial requirements, both excipients need to have controls for molecular weight distribution, related impurities, impurities, etc. that reflect the characteristics of the lots used in the critical batches.

AstraZeneca responded that they don't see the value of providing information regarding molecular weight distribution. Dr. Rogers indicated that if this is the case, they should provide justification and we will review, but to be prepared to provide this information since their justification may not be valid.

2. Does the Agency concur with the AstraZeneca strategy where control of leachables in the finished product is achieved by control of extractables from individual materials or components prior to molding or assembly by the component manufacturer?

Response

Control of extractables must be accomplished on the final molded components unless adequate justification and data are provided in the application to justify a different strategy. Adequate extractables and leachables studies must be accomplished and submitted to justify the use of the extractables vs. leachables approach, through analysis of leachables data from primary stability batches. Leachables studies must be fully completed for the primary stability batches to establish this correlation.

AstraZeneca must have possession of all methods and acceptance criteria for extractables and leachables testing for each component of the container closure. If extractables testing is justified in lieu of leachables testing, extractables testing must be accomplished periodically to verify the results obtained by the component manufacturers.

Also, you must have controls on leachables in the product specification with a note stating that the leachables content is controlled through extractables testing by the component manufacturers prior to assembly.

We are unable to comment on specific identification, reporting, or qualification thresholds since the identities of the individual extractables/leachables are unknown.

3. Does the Agency concur with the AstraZeneca strategy for control of extractables in critical container closure components and can — integrity by control through the specifications at the component suppliers?

Response

As above, the concept is generally unacceptable unless sufficient justification, validated methods, and adequate data are provided in Drug Master Files to justify this approach. Drug Master Files must be provided for each container/closure component and their raw materials.

You must have possession of all methods and acceptance criteria for extractables testing for each component of the container closure.

For the canister — testing, the ability to detect cracks and pinholes — must be validated. In the case of this testing also, you must have access to all methods and acceptance criteria for periodic testing.

4. Does the Agency concur with AstraZeneca's approach to qualifying a new supplier — for the actuator?

Response

Performance data from multiple drug product batches, as well as extractables profile data from the molded actuators, and CFR food additive references, must be provided to support the equivalency of the two actuators. Adequate information must be provided in Drug Master Files for both the — raw materials and molded actuators.

Necessary *in-vitro* performance data to establish equivalence of the actuators include spray pattern, plume geometry, particle size distribution, and dose uniformity.

Note that demonstrating "equivalence" is more stringent than just showing the raw materials meet the acceptance criteria for the above parameters

5. AstraZeneca intends to show *in-vitro* equivalence between — cans. If cans from the suppliers are shown to be equivalent, then AstraZeneca proposes not to place any product manufactured using — cans in the clinical program. Does the Agency concur with this proposal?

Response

The _____ can does not need to be qualified by inclusion into clinical trials if the extractable/residuals profile, foreign particulates profile, and in vitro performance are equivalent to the _____ can. For in-vitro performance parameters, see the previous comment.

To support the in-vitro performance, data from both accelerated and long-term stability studies are needed to access the equivalency of these two cans. Adequate information must be provided in Drug Master Files for both canisters. These supporting documents must contain sufficient information in regard to cleaning procedures, _____ composition, _____ application procedure, as well as the heat treatment procedure to support the equivalence of the two cans.

Please note that demonstrating "equivalence" is more stringent than just showing both cans meet the acceptance criteria for the above parameters.

6. Does the Agency concur with the testing proposed by AstraZeneca to satisfy the requirements of the draft FDA Guidance for Industry, Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products - Chemistry, Manufacturing and Controls Documentation (October 1998), Section IV - Drug Product Characterization Studies?

Response

Comparative stability data at 40°C/75% RH are required to qualify the _____ process. A Drug Master File is needed for each of the container and closure components.

Stability studies outside of the _____ are needed from drug product immediately after manufacture and near the end of the proposed expiration dating period.

The plume geometry must be characterized in 3-dimensions at appropriate time points after actuation.

7. Does the Agency concur with the proposal to pool data from 3 strengths to set commercial specifications?

Response

At this time, we cannot agree to this proposal. Acceptance criteria will be set by review of the data from each of the presentations and strengths separately.

The Sponsor wanted to know if this would be acceptable if they are able to show that there are no differences across strengths. Dr. Rogers indicated that in order to do this, they must demonstrate that there are no differences, attribute-by-attribute, submitted separately and make the argument for pooling of data.

Page 5

8. Does the Agency concur with this addition to the specifications for dose content uniformity within batch and through life, to be applied both for release and stability testing?

Response

Possibly. Our goal is to institute the acceptance criterion as defined in our MDI/DPI draft guidance.

Review of data from all critical batches is necessary to define the acceptance criterion.

On page 1-92, the specifications for Dose Content Uniformity each individual mean at the beginning, middle and end of canister life must meet the acceptance criterion instead of as a combined mean.

9. AstraZeneca has not included the test for valve delivery by weight in the drug product specification, as proper valve performance and valve to valve reproducibility are ensured by adequate controls during valve manufacture together with valve delivery by weight testing on valve components. Does the Agency concur with this proposal?

Response

Data from valve delivery measurements must be generated in the drug product during development. This proposal is premature until adequate data are established between nominal and actual formulation shot weights.

10. Based on the justification presented, AstraZeneca considers control of process impurities in the drug product specifications to be unnecessary in the commercial specifications. Does the Agency concur with this proposal?

Response

To provide a true indication of the impurity profile in the specification sheet, process impurities must be included in the list of related impurities in the drug product specifications along with their acceptance criteria. In addition, their levels must be included in the calculations for total related impurities. Their acceptance criteria may be denoted with a footnote and an asterisk stating that the process-related impurities are controlled in drug substance acceptance testing.

11. AstraZeneca believes that collection of up to — actuations is acceptable for the aerodynamic particle size distribution test if justified by the sensitivity of the analytical method. Does the Agency concur with this position?

Response

We disagree with the proposed — actuation concept. The number of actuations must be justified as being required according to the sensitivity of the analytical method. For this purpose, the minimum

number of actuations necessary is to be used. The analytical method must be optimized to maximize its sensitivity.

Also, the amount of drug substance deposited on the critical stages of the cascade impactor should be sufficient for reliable assay, but not so excessive as to bias the results by masking individual actuation variation.

We note that you are in the process of reducing the number of actuations. We recommend that you study the Particle Size Distribution profiles for budesonide at total deposition levels of

After further discussion, it was disclosed that the sponsor was proposing 10 actuations as a maximum and 5 actuations as the minimum as defined by the labeling for dosing. It was clarified that 10 actuations should be compared with individual stage particle size distribution data and their equivalency shown for the budesonide component.

12. Does the Agency agree that Andersen impaction data from both methodologies will be acceptable for use in shelf life generation and setting of specifications provided that equivalence is demonstrated?

Response

The calculation of expiry will use the data obtained from the more sensitive of the two methods unless equivalency of the two methods has been adequately proven. However, we have serious reservations about the use of excessive number of actuations for the budesonide component. The use of 10 actuations for the budesonide component is generally unacceptable for Andersen CI. See above comment.

Comparative data from individual stages and mass balance data must be provided to evaluate the equivalence of the two methods.

13. Does the Agency concur with the size ranges proposed for control purposes?

Response

Tests must be developed to determine the number and identity of foreign particulates less than 5 micrometers and greater than 5 micrometers and greater than 10 micrometers.

14. AstraZeneca believes that additional stability studies on the unprotected product at 25°C/75% RH are not required to demonstrate the need for the Symbiocort pMDI product. Does the Agency concur with this position?

Response

Stability studies must be conducted at 25°C/75% RH on unprotected canisters to establish the in-use

period after the protective packaging is compromised.

Protected drug product must be subjected to stability studies at 25°C/75% RH for one third of the proposed expiration dating period.

The need for better or additional _____ is a review issue. Adequate storage stability data from 30°C/60% RH, 40°C/75% RH, and 25°C/75% RH must be evaluated to draw a conclusion as to the appropriateness of the _____ processing.

15. Based on the information provided, AstraZeneca proposes to assign a shelf life for the 56 actuation physician sample pack equivalent to that assigned to the 120 actuation product. Does the Agency concur with this proposal?

Response

The assigned expiry will be based on all data available from each separate presentation. However, the whole data set will be evaluated before a conclusion can be arrived at. This is a review issue. We wish to remind you that accelerated stability studies are required also.

16. Does the Agency concur that the 56 actuation physician sample pack is approvable based on *in vitro* data only?

Response

The *in vitro* data required for the 56-actuation presentation is identical to that required for the 120-actuation presentation - see our MDI draft guidance for details. The requirement for additional clinical trials is a review issue and will depend on the data presented.

17. Is the NDA stability protocol for drug product acceptable to the Agency?

Specifically, based on the justification presented, AstraZeneca intends to place a minimum of 3 batches per product strength on storage to support the primary stability program for the 120 actuation products. One batch per strength will be placed on storage in 3 orientations, and the other 2 batches will be placed on storage valve down only. For the 56 actuation physician sample pack, if _____ strengths are required, only the outer strengths will be placed on storage using the approach outlined above; however if fewer strengths are developed, each strength will be placed on storage. Does the Agency concur with this proposal?

Response

The batch size of the "pilot-scale" batches was found to be greater than _____ while the commercial batches were stated to be _____.

Canisters from both suppliers must be represented in the stability data.

All strengths of all presentations must be placed in the stability testing program.

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18. Does the Agency concur with the approach taken by AstraZeneca for manufacture of the PQ batches?

Response

This approach is conceptually acceptable.

ADDITIONAL CMC COMMENTS

1. At this time, we are withholding comments on proposed acceptance criteria for both drug substances and the drug product since these are review issues.

Comments on budesonide drug substance are withheld owing to absence of submitted information.

Comments pertaining to the formoterol fumarate dihydrate drug substance:

2. For FFD drug substance, levels of _____ and FFD _____ must be minimized and appropriate limits set.
3. For related impurities, both the results for analyses must be reported and acceptance criteria must be stated to two significant figures.
4. For FFD micronized, conditioned drug substance, a second specific identity test must be included in the specification sheet.
5. For FFD micronized, conditioned drug substance, provide adequate test method(s) and acceptance criteria in the NDA submission on levels of polymorphic impurities. Alternatively, provide sufficient justification for not including these controls in the specification sheet.
6. The Particle Size Distribution and conditioning procedure must be adequately controlled for the

FFD micronized, conditioned drug substance. The NDA submission must contain detailed micronization and conditioning procedures with adequate controls.

7. During development in the initial batches of both FFD and FFD micronized, conditioned drug substance, the testing for Microbial Quality should be accomplished more frequently than annually.

Comments pertaining to the Symbicort pMDI drug product:

8. The critical batches of drug product must be carefully evaluated for related impurity levels, all performance parameters, etc. during the time period they are provided to patients.

9. We note that _____ proposed for use in the Phase 3 clinical trials is not the same as that proposed for the to-be-marketed product. Both these protective packages must be shown to adequately protect the drug product and must be shown to be equivalent in moisture permeation and PSD during accelerated stability testing.

10. The use of a _____ is unacceptable for in-line stress testing. The _____ stress test must immerse the canisters and valve for a sufficient time to bring the equilibrium internal temperature of all canisters to at least _____. The proposed stress testing method must be appropriately validated. If the drug product is _____ sensitive, as we conclude from your use of protective packaging, an alternative mode of heating is likely to be more suitable and should be adopted.

11. Validation data must be provided to justify the rate and frequency of propellant addition to the formulation tank containing the bulk suspension. Generally, the Master Batch Record must provide all relevant parameters pertaining to all aspects of the manufacturing process.

12. We wish to remind you that removal of stages _____ from the cascade impactor (CI) assembly possibly affect the pressure downstream from the CI stage _____ and likely needs to be compensated for to ensure the flow through the remaining stages is equivalent to that of a complete CI. Hence, before adopting such an approach, appropriate validation studies must be accomplished to show equivalence of the CI data obtained with and without these _____ stages. Equivalence of the resulting PSDs for both APIs of the drug product must be evaluated to prove this assumption is valid.

13. In the acceptance criteria for the PSD, the mass balance criterion for each active must be _____ of the label claim. It is inappropriate to eliminate this acceptance criterion from the specification.

14. The drug product leakage rate acceptance criteria are excessive and must reflect the data from all available batches.

15. Visual examination acceptance criteria need to include inspection of canister walls and other

internal surfaces for deposited drug.

16. In regard to post-manufacturing storage, the Master Batch Record must clearly identify a validated range of storage periods.

17. The stability protocol does not seem to address the stability of all presentations in all storage orientations.

18. To justify the proposed stability protocol, data must be presented which were obtained by the decision tree process presented in the draft MDI/DPI guidance.

19. The following *in-vitro* comparisons need to be made between the budesonide component of Symbicort pMDI and the budesonide HFA. These data are critical for you to have and to assure its validity prior to pursuing phase 3 clinical trials. Such data must be shared with the Agency.

19.a. Pertaining to study SD-039-0723, it is advisable that *in-vitro* dose proportionality be proven through evaluation of both Dose Uniformity data at the lowest number of actuations proposed, and through evaluation of the Particle Size Distribution data on both a stage-by-stage and Mass Balance basis (beginning to end of canister life). The PSD determinations must be accomplished using a minimum number of actuations per determination. *In-vitro* dose proportionality needs to be shown in at least 3 batches of both budesonide HFA and Symbicort pMDI. These batches must be evaluated at release and through long-term and accelerated storage stability testing over the length of time the two drugs will be administered to patients. The validity of the dose proportionality must be established at the beginning, middle and end of the canister.

19.b. Studies must be performed to characterize the number of actuations needed to prime the drug products in terms of initial priming requirements. Priming information must be used to support the related investigational labeling statements.

19.c. In-use studies must be performed to determine the recommended cleaning frequency, and the associated instructions must be included in the investigational labeling. In support of NDA filing, we recommend that MDIs used in clinical studies be sent for testing of pertinent parameters after use (dose content uniformity and the particle size distribution).

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 2, 2002

TIME: 9:00 AM

LOCATION: Parklawn, Conference Room L

APPLICATION: Symbicort™ (budesonide/formoterol) pMDI

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Representatives of Division of Pulmonary and Allergy Drug Products

Raymond Anthracite, M.D., Medical Officer
 Emmanuel Fadiran, Ph.D., Clinical Pharmacology/Biopharmaceutics Team Leader
 Robin Huff, Ph.D., Supervisory Pharmacologist
 Lisa Kammerman, Ph.D., Biostatistics Team Leader
 Marianne Mann, M.D., Deputy Division Director
 Robert Meyer, M.D., Division Director
 Guirag Poochikian, Ph.D., Chemistry Team Leader
 Timothy Robison, Ph.D., Pharmacologist
 Brian Rogers, Ph.D., Chemist
 Sandra Suarez, Ph.D., Clinical Pharmacology/Biopharmaceutics Reviewer
 Anthony Zeccola, Regulatory Management Officer

Representatives of AstraZeneca

Nola Bowles, BSc., Associate Director, Analytical Development
 Ann Brindley, Ph.D., Associated Director, Analytical Development
 Eric Couture, Ph.D., Director, Regulatory Affairs
 Michael Gillen, Director, Clinical Pharmacology
 William Mezzanotte, M.D., Director, Clinical Research
 Andy Rignall, Ph.D., Manager, Analytical Development
 Liuda Shtohryn, Pharm.D., Associate Director, Technical Regulatory Affairs
 James Sullivan, Manager, Regulatory Affairs
 Rob Whyard, BSc., Associate Director, Pharmaceutical Project Management

BACKGROUND: This meeting was held in response to a January 16, 2002 End of Phase 2 Meeting Request. Based on the number of questions that were included the Sponsor requested two meetings, one for CMC related questions and the other to include preclinical and clinical questions. These minutes are documentation of the preclinical and clinical discussion, the CMC discussion is documented in another correspondence.

Pharmacology/Toxicology

- 1. Does the Agency concur that the completed/ongoing preclinical pharmacology/toxicology studies with both the monoproducts and the combination support the proposed clinical program? Specifically:**

Does the Agency concur that toxicology data derived from excipients used in the completed long-term studies with another AstraZeneca compound _____ in rats and dogs support the use of a similar HFA-227 pMDI formulation in the proposed phase 3 clinical program and registration?

From a preclinical standpoint, data derived for excipients, PVP K-30 and PEG-600, from studies _____ in rats appear to support the use of a similar formulation with the Symbicort drug product.

Does the Agency concur that toxicology/pharmacokinetic data obtained with budesonide/formoterol pMDI combinations are sufficient to support clinical trials with budesonide HFA-227 pMDI and registration of Symbicort pMDI?

Given that the Symbicort and budesonide HFA pMDI formulations are essentially identical with the exception of the presence of formoterol in Symbicort, preclinical studies with the Symbicort HFA pMDI formulation are sufficient to support clinical trials with the budesonide HFA pMDI formulation.

Does the Agency concur with the AstraZeneca strategy where control of leachables in the finished product is achieved by control of extractables from individual materials or components prior to molding or assembly by the component manufacturer?

Please clarify what batches of the Symbicort HFA pMDI formulation were used in the 90-day preclinical toxicology studies with rats and dogs (i.e., were the cannisters near the expiration date?).

This information may assist in determining whether exposure to extractables/leachables in these studies is sufficient for qualification.

All extractables/leachables should be assessed for mutagenic or carcinogenic potential, including the presence of structural alerts.

For extractables/leachables that are carcinogenic or mutagenic, inhalation exposure-based risk assessments should be provided.

Clinical Pharmacology/Biopharmaceutics

1. Does the Agency agree that the proposed pharmacokinetic program is sufficient to support the registration of Symbicort pMDI?

- a. We agree that study SD-039-0723 will determine whether the plasma concentrations of budesonide and formoterol produced by the three different formulations of Symbicort pMDI are proportional with the labeled dose.

However, since no information is available on the PK of budesonide/formoterol from the Symbicort pMDI formulation in asthmatic adults and children, the sponsor is encouraged to assess the PK and/or the PD of these two drugs at steady state following administration from the Symbicort pMDI in asthmatic subjects ages 6 years and above.

This PJ/PD study may be conducted as a subgroup analysis from studies 0715, 0716, 0717, 0718 and/or 0729.

- b. The results from PK study SD-039-0626 are questionable. The sponsor is encouraged to confirm these findings in the proposed safety study 0719 by assessing the PK and/or PD of budesonide/ formoterol in a subgroup of patients.
- c. The design (treatments) described below is suggested for study protocol SD-039-0723 (inter-device dose proportionality study).

Study treatments

- Symbicort pMDI 40/4.5 mcg/actuation, sixteen actuations
- Symbicort pMDI 80/4.5 mcg/actuation, eight actuations
- Symbicort pMDI 160/4.5 mcg/actuation, four actuations

You should report 90% Confidence Intervals (CI) for the ratio of the geometric means of the PK parameters between treatments.

It is also suggested that the you apply the power model analysis for comparability of all strengths.

Note: You are encouraged to assess the *in vitro* dose proportionality among strengths. It is recommended that the *in vitro* study should be conducted first.

- d. It is not clear from the summary protocols provided, which formulation/device of Oxis Turbuhaler will be used in the proposed PK studies. Please clarify.

Clinical/Statistical

Comment Responses Requiring Clarification

This section includes selected FDA comments made about the original IND safety submission (10/5/2001, N-000), AstraZeneca responses to them and the most recent Agency thinking on the topic.

1. It is noted that none of the submitted protocols are finalized. Final protocols are promised after the EP2 Meeting.

We have been working with the sponsor toward a way of handling protocol amendment submissions of fairly complete draft protocols and final protocols. Regrettably, this has failed. Examination of the changes documented by AstraZeneca and the changes actually made to the amended draft protocols showed that the former was a subset of the latter. We can no longer support detailed commentary on protocols that are not final in form.

2. An opportunity to record AEs in patient diaries daily should be added as an aid to reporting them at study visits.

A patient notebook - separate from the electronic diary used to capture efficacy data and compliance - will be provided to patients to aid them in recording health problems experienced between study visits.

The current plan to issue each patient a notebook for the purpose of recording AEs and treatments is likely to result in a lot of misplaced and forgotten notebooks. If there is any way these can be built into the PDA it would be more convenient for the patient and vastly improve adverse event and compliance reporting. AstraZeneca said that they had given a lot of thought to this and just couldn't incorporate these extra tasks into the PDA. We suggested that an alternative would be to balance the amount of material recorded by paper and PDA means. This would equalize the importance of both recording methods to the patients making it more likely that both would be maintained.

3. Twenty-four hour Holter monitoring should also be obtained in a subset at baseline and after about 2 weeks of treatment to avoid losing data because of the aforementioned anticipated high dropout rate later in the study.

The protocols will be amended accordingly...It is anticipated that approximately 100 to 120 subjects in formoterol-containing treatment groups (i.e. Oxis or Symbicort) will take part in Holter monitoring.

We are more specifically interested in having 300 patients with Holters, 200 of whom are exposed to the Fixed-Dose Symbicort HFA pMDI formulations.

4. Pharmacokinetic sampling should be built into the three pivotal trials (0716, 0717, 0718) to reassure us of comparable systemic exposure to formoterol and budesonide by these many devices and formulations.

Study 0723 will determine whether the plasma concentrations of budesonide and formoterol produced by the three different formulations of Symbicort pMDI are proportional with the labeled dose. As agreed by the Agency in the December 18, 2001 teleconference, no further pharmacokinetic sampling would be required in the pivotal trials.

We were given information that PK studies in the three pivotal clinical trials would not be feasible due to limits of measurement for both budesonide and formoterol. Our BioPharm specialists have a different opinion and express it in the appropriate section of these minutes.

Sponsor Queries & Responses To Them

1. **Does the Agency agree that the responses provided in this submission sufficiently address all 15 draft comments?**

See last section, "Comment Responses Requiring Clarification."

2. **Does the Agency agree with the doses chosen for the Fixed-Dosing Phase 3 program?**

Our sense is that there is insufficient data to choose any dose of either component for the Symbicort pMDI formulation. We hastened to add that methodical dose selection is not a requisite criteria for drug development, but that it is a risky strategy

3. **Will the design of the Fixed-Dosing program support the registration of the three Symbicort pMDI total daily fixed doses, each indicated in patients aged 6 years and above?**

Approval (registration) will be a review issue. Please see the response to question #2.

- 4A & B. **Does the Agency agree with the proposed objectives, design, treatments, doses and**

analysis methods chosen for 0729?

We will review this in detail when a final protocol has been submitted. Protocol 729 will require an additional arm (placebo Oxis and active budesonide) to provide credible results, and will also require Symbicort and Oxis arms with 2 inhalations/actuations to demonstrate dose sensitivity. A non-inferiority comparison is not required and is inappropriate for the amount of reviewed information on these formulations. AstraZeneca spoke against adding both a 2-inhalation/actuation arm and arms with concomitantly administered placebo formoterol and active budesonide matched to each of the Symbicort budesonide doses. We suggested that the 4 inhalation/actuation arm could be eliminated and that the placebo-formoterol-active-budesonide arm could match only one of the Symbicort budesonide dose arms. AstraZeneca specifically requested more dialogue on the development of this protocol and we concurred.

5. Does the Agency agree that the number of patients treated in the Fixed and Adjustable Dosing Programs for Symbicort pMDI will be sufficient to support the safety assessment?

The minimum numbers of patients required for safety assessment are set by the ICH guidelines as well as by safety signals that will arise during drug development. It is premature to address this issue because of the dearth of submitted safety data.

6. Does the Agency agree with the comparator groups for the Fixed-Dosing program in adults and children?

We continue to have reservations about this entire drug development program which we have shared with you. The results of trial 0718 will be more credible with the inclusion of a placebo arm. We offer the strongest encouragement to you to show that Symbicort HFA pMDI has \leq the efficacy of both comparator mono-products administered together in another arm of at least one clinical study. This would go a long way toward eliminating pharmaceuticals as the source of therapeutic benefit of the combination over the mono-products and could most easily be accomplished by adding an extra arm to 0716.

Our request for a placebo arm in this study of children met with resistance. This was a topic with which AstraZeneca had wrestled in the past and thought that they had settled. After much discussion, sources of the opposition to a placebo group were identified as IRBs and clinical investigators. The absence of a placebo group influences the degree of difficulty in demonstrating efficacy, but it does not abrogate AstraZeneca of responsibility to succeed in that demonstration. AstraZeneca has set about a difficult task in combining "switch" and "combination" drug development policies. It is not surprising that they are experiencing some difficulties.

7A & B. Does the Agency agree with the primary endpoints and primary comparisons chosen for pivotal Fixed-Dosing studies in adults and children and does sequential hypothesis testing adequately control for the Type I Error?

The endpoints could work to your advantage or fail completely, depending upon the correctness of your dosing assumptions and the outcome of all studies. Please see responses to queries #4 and #6. Biostatistics will address the adequacy of sequential hypothesis testing to control for the Type I Error.

8. Does the Agency agree with the analytic plan for 0716, 0717 and 0718?

See Biostatistics comments in these minutes.

9. Does the Agency agree with analysis of the co-primary endpoint of 0716 and 0717?

See Biostatistics comments in these minutes.

10. Does the Agency agree with the data set to analyzed in 0717 and 0718?

See Biostatistics comments in these minutes.

11. Does the Agency agree that modifications of 0719 will provide an adequate growth suppression study in children?

We will review this in detail when the final protocol is available to us. A draft guidance is available to aid in your development of this protocol www.fda.gov/cder/guidance/index.htm.

12. Does the Agency agree that Adjustable Dosing trials 0725 and 0726 as outlined are reasonable to support the a once-daily dosing regimen? (Tab 8, Pp 58-9)

The entire Adjustable-Dosing concept is an unprecedented labeling claim that should be considered separately from approval of the Fixed-Dose program. If this question is to be resubmitted, please provide final protocols for our review. AstraZeneca rephrased their corporate needs as wanting to know if we would dismiss adjustable-dosing out of hand. Bob Meyer (Division Director) said that we would not refuse to consider it.

13. In the Adjustable-Dosing program, does the Agency agree that trials 0727 and 0728 are reasonable in design to support the use of four actuations twice daily for periods of up to four weeks?

See the response to question #12.

14. Is the proposed scheme for reporting adverse events to various INDs and NDAs acceptable?

This is a pre-NDA meeting question.

15. Does the Agency agree that sub-population results will be reported only in the ISS and ISE?

This is a pre-NDA meeting question.

16. Does the Agency agree with line listings of adverse event reporting for Oxis Turbuhaler and absence of this information from the ISS and ISE? Does the Agency agree that no data from the Pulmicort NDA will be included in the Symbicort pMDI NDA?

This is a pre-NDA meeting question.

17. Would the Agency agree to issue a WR for Symbicort?

At some future time we might agree to this.

Biostatistics Comments

Proposed analysis of AUC: ANCOVA with subjects, period and treatment as fixed effects, and covariate of pre-dose FEV₁ from each visit. AUC will be calculated above pre-dose FEV₁ at that visit

- Explain use of pre-dose FEV₁ both as covariate and in calculating AUC
- Consider using first visit pre-dose FEV₁ as the value to calculate all AUCs. Then, use ANOVA; do not need pre-dose FEV₁.
- Tests for interactions

Sequential approach for hypothesis testing:

- Must show combination treatment is better than each component. Therefore, the initial step addresses this regulatory question.
- Define the regulatory questions the subsequent steps address.

Analysis Approach

- Include the variables used to stratify the randomization
 - If randomization is within centers, include center and center-by-treatment in models.
 - If randomization is stratified on other variables (e.g., age), include stratum and

stratum-by-treatment in models.

- Withdrawals due to asthma exacerbation: compare *proportions* of subjects who withdraw, instead of time-to-withdrawal.

Additional Global Comments Provided by Dr. Mann

1. In vitro support for the comparability of the budesonide component of Symbicort pMDI to Budesonide pMDI is necessary.
2. Support for the comparability of the formoterol component of Symbicort pMDI to Formoterol Oxis TBH needs to be provided. Trial 729 is a critical phase 2 trial that attempts to establish this.
 - A 2 puff arm of each product should be added to this trial. For example, within the same product arm, what is the ability of the chosen FEV-1 AUC endpoint to distinguish between placebo, 1 puff, 2 puffs and 4 puffs?
 - A budesonide alone arm should be added to assure that treatment with a single dose of budesonide alone does not significantly affect the FEV-1 AUC.
 - We disagree that this can be called a traditional “non-inferiority” trial since such a trial first needs to establish consistency of effect for each active product over placebo in many controlled trials, something which has not been established for either product. The purpose of this trial is to establish how comparable the foradil component of Symbicort is to a comparable dose of foradil administered on the endpoint of FEV-1 AUC.
 - We cannot agree that the chosen endpoint of 12-hour-FEV-1 AUC/adjusted over time will establish the comparability of formoterol TBH to Symbicort if the lower bound of the 95% CI for a difference is set at δ . Support for this distinction should be provided. Such support may come from comparisons within the same study arms of 1 puff, 2 puffs, and 4 puffs of Formoterol TBH or Symbicort.
 - The proposed washout period for this study is inappropriate for a drug with a prolonged half-life like formoterol. A washout period minimum of 3 days is recommended.
 - Trial 729 should include pharmacokinetic measurements to (hopefully) validate the previous results in healthy subjects that suggest that formoterol in Symbicort is, if anything, less systemically bioavailable than the formoterol in Oxis TBH. This PK aspect of the trial will be also considered relevant in judging the ultimate results of the pharmacodynamic comparability of the two products.
3. Trial 716 in children age 6-11 and adults 12 and older will separate out the primary efficacy analysis to be in adults 12 and older. While acceptable, we will want to see efficacy results

displayed in the children age 6-11 enrolled into this trial.

4. Trial 718 is the pivotal trial in children, and uses a primary efficacy endpoint of PEFr. While acceptable, we would like FEV-1 assessments to be determined in this study and would like results of FEV-1 as an important secondary endpoint.
5. We highly recommend that at least one of the proposed phase 3 trials (716, 717, or 718) should include a treatment arm of formoterol OXIS TBH with Budesonide pMDI taken together as individual ingredients. Such a treatment arm provides invaluable perspective on addressing the concerns about pharmaceutical differences between Symbicort and the individual treatment arms.
6. As mentioned previously, the three pivotal 12-week trials include three different doses of Symbicort all studied in varying patient populations. While the program could succeed in supporting the approval of Symbicort, it is vulnerable to any one trial failing.
7. We do not feel we can comment meaningfully on the adjustable dosing program without first seeing results from a fixed dose regimen.
8. This is your EOP-2 meeting request, which we have separated out into two separate 1.5 hour meetings, one for clinical/biopharm/preclinical issues and one for chemistry issues. Additional meeting requests (other than of course a pre-NDA meeting request) may not be able to be granted. Keeping your questions specific, precise, and limited in scope is highly recommended in this regard.

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/s/

Anthony Zeccola
3/30/03 03:28:25 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-929	Efficacy Supplement Type SE-	Supplement Number
Drug: Symbicort® (budesonide/formoterol) MDI		Applicant: AstraZeneca
RPM: Colette Jackson	HFD-570	Phone # 6-1230
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority 	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
<ul style="list-style-type: none"> • Chem class (NDAs only) 	4	
<ul style="list-style-type: none"> • Other (e.g., orphan, OTC) 		
❖ User Fee Goal Dates		
7/23/2006		
❖ Special programs (indicate all that apply)		
<input checked="" type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2		
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee 	<input checked="" type="checkbox"/> Paid UF ID number <u>3006208</u>	
<ul style="list-style-type: none"> • User Fee waiver 	<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)	
<ul style="list-style-type: none"> • User Fee exception 	<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)	
❖ Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> • Exclusivity summary- 7/21/2006 • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	12/5/2005

General Information	
❖ Actions	
• Proposed action	(x) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(x) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(x) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(x) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	7/20/2006
• Original applicant-proposed labeling	9/23/2005
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	5/2/2006 and 5/19/2006
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	7/20/2006, 7/11/2006, 6/16/2006, and 9/23/2005
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	11/29/2005, 12/6/2005 (2) 12/27/2005, 1/10/2006, 2/9/2006, 3/3/2006, 3/8/2006, 3/13/2006, 3/20/2006, 4/4/2006, 4/12/2006, 4/28/2006 (2), 5/4/2006, 5/10/2006, 5/24/2006, 6/8/2006, 7/5/2006, 7/17/2006, and 7/20/2006.
❖ Memoranda and Telecons	3/28/2006 (Minutes faxed 4/25/2006)
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	4/2/2002 and 4/4/2002 (CMC)
• Pre-NDA meeting (indicate date)	6/28/2004 and 11/1/2004 (CMC)
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	

❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (<i>indicate date for each review</i>)	CMC-7/19/2006 P/T- 5/26/2006 DD- 7/21/2006
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	11/10/2005, and 6/5/2006
❖ Microbiology (efficacy) review(s) (<i>indicate date for each review</i>)	
❖ Safety Update review(s) (<i>indicate date or location if incorporated in another review</i>)	In 6/5/2006 MO Review
❖ Risk Management Plan review(s) (<i>indicate date/location if incorporated in another rev</i>)	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	12/5/2005
❖ Demographic Worksheet (<i>NME approvals only</i>)	
❖ Statistical review(s) (<i>indicate date for each review</i>)	5/23/2006 and 6/12/2006
❖ Biopharmaceutical review(s) (<i>indicate date for each review</i>)	11/4/2005 and 5/23/2006
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date for each review</i>)	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) (<i>indicate date for each review</i>)	12/7/2005, 4/24/2006, and 7/19/2006
❖ Environmental Assessment	
• Categorical Exclusion (<i>indicate review date</i>)	4/24/2006
• Review & FONSI (<i>indicate date of review</i>)	
• Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (<i>indicate date for each review</i>)	
❖ Facilities inspection (provide EER report)	Date completed: 6/30/2006 (x) Acceptable () Withhold recommendation
❖ Methods validation	() Completed (x) Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	11/18/2005 and 5/22/2006
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	
❖ CAC/ECAC report	

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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/s/

Colette Jackson
7/21/2006 02:52:25 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-929

Supplement #

SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: SYMBICORT ®

Generic Name: budesonide/formoterol inhalation aerosol

Dosage Form: Metered Dose Inhaler

Strengths: 80/4.5 mcg, and 160/4.5 mcg

Applicant: AstraZeneca Pharmaceuticals

Date of Application: September 23, 2005

Date of Receipt: September 23, 2005

Date clock started after UN: N/A

Date of Filing Meeting: November 9, 2005

Filing Date: November 22, 2005

Action Goal Date (optional): July 9, 2006

User Fee Goal Date: July 23, 2006

Indication(s) requested: Asthma

Type of Application: Original (b)(1) NDA Original (b)(2) NDA _____
(b)(1) Supplement _____ (b)(2) Supplement _____
[If the Original NDA was a (b)(2), all supplements are (b)(2); if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or a (b)(2).]

NOTE: If the application is a 505(b)(2) application, complete the 505(b)(2) section at the end of this summary.

Therapeutic Classification: S P _____
Resubmission after a withdrawal? No Resubmission after a refuse to file? No
Chemical Classification: (1,2,3 etc.) 4
Other (orphan, OTC, etc.) No

User Fee Status: Paid Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee ID # 3006208

Clinical data? YES NO, Referenced to NDA # Monograph _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES xNO

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? YES xNO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES xNO
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

• Does the submission contain an accurate comprehensive index? xYES NO

• Was form 356h included with an authorized signature? xYES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

• Submission complete as required under 21 CFR 314.50? xYES NO
If no, explain:

• If an electronic NDA, does it follow the Guidance? xYES NO
If an electronic NDA, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Modules 1 through 5 were submitted electronically.

Additional comments:

Module 1 provided also in paper.

• If in Common Technical Document format, does it follow the guidance? xYES NO

• Is it an electronic CTD?(**eCTD not currently available**) xYES NO
If an electronic CTD, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?
All parts were submitted in electronic format.

Additional comments:

• Patent information included with authorized signature? xYES NO

• Exclusivity requested? xYES, 3 years NO
Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

• Correctly worded Debarment Certification included with authorized signature? xYES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as "To the best of my knowledge"

• Financial Disclosure information included with authorized signature? xYES NO
(Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)

• Field Copy Certification (that it is a true copy of the CMC technical section)? xYES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? xYES NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
- List referenced IND numbers: IND 63,394 and _____ .
- End-of-Phase 2 Meeting(s)? Date(s) _____ xNO
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s) xYES Date(s) _9/8/04 (CMC), 12/6/04_
 If yes, distribute minutes before filing meeting.

Project Management

- Package insert consulted to DDMAC? xYES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? xYES NO
- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support? xN/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? xN/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support? xN/A YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? xN/A YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? xYES NO
 If no, did applicant submit a complete environmental assessment? YES NO
 If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? xYES NO

- If parenteral product, consulted to Microbiology Team (HFD-805)? YES xNO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.) YES NO
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9). YES NO
- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9). YES NO
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

___ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

___ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

___ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

___ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

___ 21 CFR 314.50(i)(1)(ii): No relevant patents.

___ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

___ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

_____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:
 - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

	YES	NO
--	-----	----
 - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

	YES	NO
--	-----	----
 - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

	N/A	YES	NO
--	-----	-----	----
 - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

	N/A	YES	NO
--	-----	-----	----
- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):
 - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

	YES	NO
--	-----	----
 - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

	YES	NO
--	-----	----
 - EITHER
The number of the applicant's IND under which the studies essential to approval were conducted.

	YES, IND # _____	NO
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OR

 A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

	N/A	YES	NO
--	-----	-----	----
- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

	YES	NO
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ATTACHMENT

MEMO OF FILING MEETING

DATE: November 9, 2005

BACKGROUND:

SYMBICORT ® is a budesonide/formoterol combination product. IND 63,394 is the referenced IND for SYMBICORT ®.

Attendees:

Badrul A. Chowdhury, M.D., Ph.D., Division Director, DPADP
Peter Starke, M.D., Clinical Team Leader, DPADP
Harry Gunkel, M.D., Clinical Reviewer, DPADP
Timothy Robison, Ph.D., Pharmacology/Toxicology Reviewer
Joseph Sun, Ph.D., Pharmacology/Toxicology Team Leader
Ted Guo, Ph.D., Statistical Reviewer
Ruthanna Davi, Ph.D., Statistical Team Leader
Alan Schroeder, Ph.D., Review Chemist
Colette Jackson, Project Manager

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Harry Gunkel
Secondary Medical:	Peter Starke
Statistical:	Ted Guo
Pharmacology:	Timothy Robison
Statistical Pharmacology:	
Chemist:	Alan Schroeder
Environmental Assessment (if needed):	
Biopharmaceutical:	Sayed Al Habet
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Regulatory Project Manager:	Colette Jackson
Other Consults:	DDMAC- Michelle Safarik DMETS

Per reviewers, are all parts in English or English translation? xYES NO
If no, explain:

CLINICAL FILE X REFUSE TO FILE _____

- Clinical site inspection needed: YES xNO

- Advisory Committee Meeting needed? YES, date if known _____ xNO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

		xN/A	YES	NO
CLINICAL MICROBIOLOGY	FILE _____	REFUSE TO FILE _____		xN/A
STATISTICS	FILE <u>X</u> _____	REFUSE TO FILE _____		
BIOPHARMACEUTICS	FILE <u>X</u> _____	REFUSE TO FILE _____		
	• Biopharm. inspection needed:		YES	xNO
PHARMACOLOGY	FILE <u>X</u> _____	REFUSE TO FILE _____		
	• GLP inspection needed:		YES	xNO
CHEMISTRY	FILE <u>X</u> _____	REFUSE TO FILE _____		
	• Establishment(s) ready for inspection?	xYES	NO	
	• Microbiology	YES	NO	xN/A

ELECTRONIC SUBMISSION:
 Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

- _____ The application is unsuitable for filing. Explain why:
- X_____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.
- _____ No filing issues have been identified.
- X_____ Filing issues to be communicated by Day 74.

ACTION ITEMS:

1. Document no filing issues conveyed to applicant by Day 74.

Colette Jackson
Regulatory Project Manager, HFD-570

**Appears This Way
On Original**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Colette Jackson
12/5/2005 01:54:53 PM
CSO