

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-949

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology and Biopharmaceutics Review (FINAL)

NDA: 21-949

Date of Submission: September 12, 2005

<u>Generic Name</u>	Budesonide Inhalation Powder
<u>Brand Name:</u>	Pulmicort Turbuhaler ®
<u>Formulations:</u>	Inhalation Powder
Route of Administration:	Oral Inhalation
Indication:	Asthma
<u>Type of Submission:</u>	Post-marketing Commitment (Study Reports for NDA 20-441)
<u>Sponsor:</u>	AstraZeneca
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader	Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.

Recommendation:

From the clinical pharmacology perspective, this supplemental NDA is acceptable.

Executive Summary:

This is a Phase 4 commitment to improve the dose content uniformity and the performance of the Pulmicort based on the approval letter dated June 24, 1997 for the first version of the inhaler (**M0 or version A**). The second version of the inhaler utilizing the enhanced spheronization process (ESP) was approved in December 2000 (**MO-ESP or version B**). The new version that is submitted in this NDA (**M3 or version C**) is an improvement of the existing version. The improvement was made by adding lactose as an excipient to improve product performance as well as modification of mouthpiece, dose indicator, and number of dose per device.

To establish the link between the three versions, the sponsor submitted the following main studies/analysis:

- Pivotal PK study (#601) to establish the link between M3 and M0.
- PK study to establish the link between M0 and M0-ESP (study # 708)
- Phase 3 studies (620 and 726) including PK in a small subset of patients using M3 and M0-ESP devices.
- A cross-study comparison between study 601 (M3 vs M0) and 708 (M0 vs M0-ESP).
- Pop PK analysis of several studies.

From all studies and analysis, it can be concluded that the three versions produce comparable systemic exposure. Specifically, M3 device produce comparable or lower systemic exposure than MO-ESP. The data from these studies is briefly described below:

From study 601, the 90% CIs for the ratios of the PK parameters were within 80 to 125% for M0 (A) and M3 (C) (**Table I**). The plasma concentration time-Profiles were superimposed for M0 and M3 (**Figure I**). Similarly, the 90% CIs for the ratios of the PK parameters from study 708 was within 80% to 90% for M0 and M0-ESP.

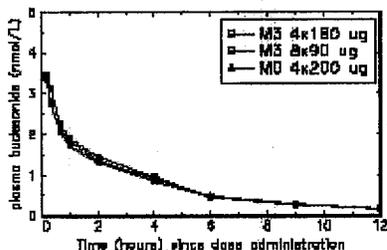
Table I. Relative Bioavailability (Study # 0601)

Treatment ratios	AUC		Cmax	
	Ratio (%)	90% CI	Ratio (%)	90% CI
M3 4 x 180 µg/M0 4 x 200 µg	96.3	90.9, 102.1	100.4	92.1, 109.4
M3 4 x 180 µg/M3 8 x 90 µg	92.2	87.0, 97.7	94.4	86.6, 102.9

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Figure I. Mean PK Profiles

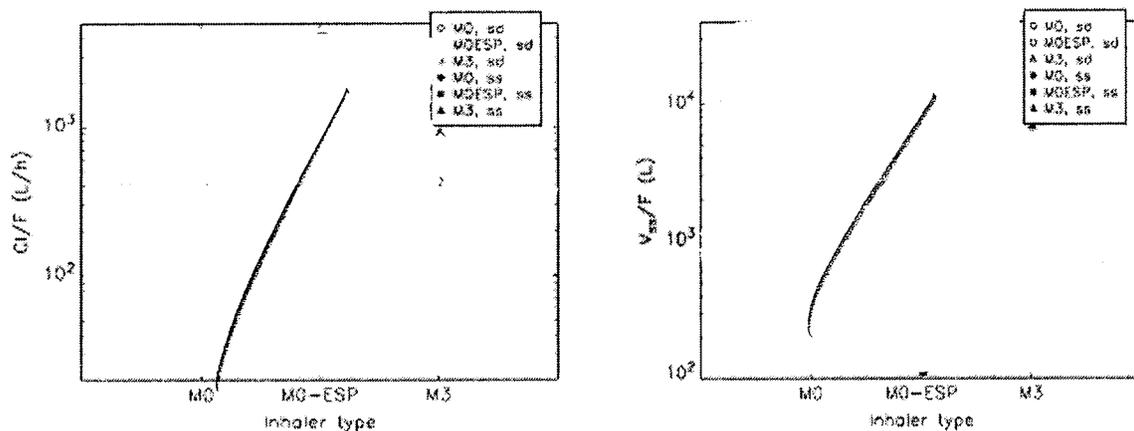


Furthermore, across studies comparison and pop PK analysis demonstrate similar exposure between M3 and M0-ESP (**Figure II**) and among the three versions of inhalers (**Figure III**). Also, the 90% CIs for the ratios of the PK parameters for the three products were within 80 to 125% (**Table II**).

Figure II. Individual AUC and Cmax Values of Budesonide for M3 and M0-ESP Expressed as Percent of Corresponding Parameter After Administration of Budesonide via M0

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Figure III. Pop PK Analysis: Effect of Inhaler Type on Apparent Clearance (Cl/F) and Volume of Distribution (Vss/F) (Exposure from M0-, M0-ESP, and M3)



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Table II. Bioequivalence Tests Between M3 (Study 601) and M0-ESP (Study 708)

Parameter	M3/M0	M0-ESP/M0	M3/M0-ESP	90% confidence limits
AUC _{0-12h} (%)	96.54	99.46	97.07	(89.74 to 105.00)
C _{max} (%)	101.01	101.06	99.95	(88.05 to 113.47)

The data from a subset of patients from Phase III studies are inconclusive, yet are important. Considering of the high variability in the data and the small number of subjects (2 to 13) in each treatment arm the data demonstrate that the systemic exposure with M3 is comparable or lower than M0-ESP. These data cannot be ignored and are useful to establish the link between efficacy and product performance/systemic exposure. Since M3 produces comparable or lower (not higher) systemic exposure than M0-ESP there are no known systemic safety concerns. This aspect of the relationship is discussed in more details in the Medical officer's review.

Conclusions:

Considering all studies and the data analysis it can be concluded that the three versions (M0, M3, and M0-ESP) produce comparable systemic exposure. Specifically, the new version (M3) may produce slightly lower systemic exposure than the currently marketed version (M0-ESP). Therefore, there are no safety concerns. Patients may be monitored for adequate response and dose adjustment may be necessary on case by case basis.

Reviewer

Sayed (Sam) Al Habet, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Clinical Pharmacology and Biopharmaceutics 2

Final version signed by Emmanuel Fadiran, R.Ph., Ph.D., Team Leader-----

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Background:

In this submission, the sponsor submitted study reports and analysis to fulfill the postmarketing/Phase 4 commitment to the original product Pulmicort Turbuhaler (budesonide inhalation powder, NDA 20-441). Other related NDAs were also referenced by the sponsor. These are NDA 21-929 for Pulmicort Respules (budesonide inhalation suspension), NDA 20-746 for Rhinocort Aqua (budesonide nasal spray), and NDA 21-324 for Entocort EC (budesonide) capsules. NDA 20-441 for Pulmicort Turbuhaler was approved in June 24, 1997 with the following Phase IV commitment:

“You will conduct an ongoing development program for Turbuhaler which includes modifications of Turbuhaler, the process of controlled aggregation of micronized budesonide, the powder composition, and possible clinical testing”

Product's Versions:

1. **M0**: This is the original version of Pulmicort Turbuhaler (NDA 20-441) approved on June 24, 1997.
2. **M0-ESP**: Modified version that utilized Enhanced Spheronization Process (ESP). This was submitted under S-009/NDA 20-441. This was approved in December 8, 2000.
3. **M3**: New version submitted to the current NDA. This version will replace the currently approved version (M0-ESP). The sponsor intends to discontinue marketing the existing version. The M3 version will be available in the following strengths/packageing:
 - 90 mcg/inhalation that delivers 80 mcg of budesonide per inhalation ex-mouthpiece (60 inhalations)
 - [REDACTED]
 - 180 mcg/inhalation delivering 160 mcg budesonide per inhalation, ex-mouthpiece (120 inhalations).

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It should be noted, however, that the sponsor intends to market **only two** of the above strengths/packages. These are the 90 mcg (i.e., 80 mcg delivered dose) and 180 mcg (i.e., 160 mcg delivered dose) per inhalation containing 60 and 120 inhalations, respectively.

Historical Regulatory Perspective:

The following are the major historical interactions with the sponsor on this product:

- M0 the original Pulmicort Turbuhaler was approved in June 24, 1997 (NDA 20-441).
- M0-ESP was approved in December 8, 2000 (NDA 20-441/S-009)
- M3 clinical program started with a new IND 63,762 that was submitted on December 7, 2001.

The currently marketed version is available as dry powder containing only the active ingredients (budesonide). In the new version (M3), lactose was added as an excipient to improve product

performance. In addition, there were some modifications to the device involving the following: mouth mouthpiece, dose indicator, and number of dose per device.

What Studies Have Been Submitted?

Pivotal PK Study:

From the clinical pharmacology perspective, study SD-005-0601 is the pivotal PK study that was submitted by the sponsor. This study was conducted to establish the bioavailability of budesonide when administered with the to-be-marketed version, M3 inhaler, relative to the original version, M0 inhaler.

Supportive Studies (600 and 708):

Two additional studies were submitted. The first is study # SD-004-0600 focusing on the relative systemic exposure and plasma cortisol suppression using two device versions, M0 and M0-ESP. The second study is # SD-004-0708 which was conducted to establish the relative systemic exposure of the new (M0-ESP) device and the originally approved device (M0). These two studies, 600 and 708, were completed in 1998/99 and were part of 1999/2000 submission. It should be noted that 708 was a pivotal PK study in 1999 submission for the approval of M0-ESP device along with other CMC data. Since these studies were previously submitted, the sponsor provided only two pages synopsis for each study in this submission.

A Cross-studies Comparison (601 vs 708):

The sponsor conducted a *post hoc* cross-study comparison between M3 PK data from Study # 0601 and M0-ESP data from study # 0708. Finally, a population PK analysis report was submitted as supportive data analysis.

Pivotal Phase III Study (PK Subset):

In two Phase 3 pivotal clinical studies PK samples were collected in a small subset of patients of approximately 8 subjects from each parallel treatment arms. Study # SD-004-0620 was conducted in adults and adolescents and study SD-004-0726 was conducted in children. Furthermore, the sponsor submitted two additional clinical studies (#04-3020 A and 04-3023A) that were submitted in the original NDA 20-441 in support the current NDA.

The focus of this review is on the following studies: 601, 708, 620, and 726 as well as pop PK analysis.

Summary of Individual Studies:

Study SD-005-0601 (Pivotal PK Study):

Objective: To determine the relative bioavailability of budesonide following M3 180 mcg and M0 200 mcg and to determine the dosage strengths equivalence of M3 180 mcg and M3 90 mcg.

Design: This was 3-way crossover in 37 asthmatic patients (males and females) as follows:

- Treatment A (640 mcg): M3 180 mcg x 4 inhalation (720 mcg)
Actual dose: 160 mcg per inhalation x 4 = 640 mcg.
- Treatment B (640 mcg): M3 90 mcg x 8 inhalation (720 mcg)
Actual dose: 80 mcg per inhalation X 8 = 640 mcg.
- Treatment C (640 mcg): M0 200 mcg x 4 inhalation (800 mcg)
Actual dose: 160 per inhalation x 8 = 640 mcg.

Plasma PK samples were collected over 12 hours for the determination of budesonide concentrations.

Results:

- The PK parameters and the plasma concentration-time profiles following the three treatments were comparable (**Table 1 and Figure 1**).
- The 90% CIs for the ratios C_{max} and AUC were within 80% to 125% for all treatments (**Table 2**).
- The ratios for M3/M0 for both C_{max} and AUC were about 100% (96% to 100%).
- For dosage strength, the ratio of M3 (4 x 180 mcg /M3 8 x 90 mcg) were around 93% for C_{max} and AUC (92% to 94%).

Table 1. Mean PK Parameters (Study # 0601)

Treatment	Parameter	C _{max} [†] (nmol/L)	AUC [†] (nmol*min/L)	C _{12h} [†] (nmol/L)	T _{max} (min)	MRE (h)	T _{1/2} [†] (h)
M3 4x180 ug (N = 36)	Mean*	3.32	569	0.144	11.7	4.6	3.8
	Std*	31	23	34	3.8	0.8	23
	Min	1.73	311	0.05	10	3	2
	Median	3.37	583	0.14	10	4	4
	Max	6.38	823	0.29	20	6	6
M3 8x90 ug (N = 36)	Mean*	3.54	619	0.151	13.3	4.5	3.5
	Std*	33	23	36	4.8	1.2	26
	Min	2.31	420	0.08	10	3	3
	Median	3.10	605	0.15	10	4	3
	Max	7.37	874	0.34	20	11	10
M0 4x200 ug (N = 36)	Mean*	3.28	589	0.147	13.6	4.7	3.7
	Std*	39	29	47	9.9	0.9	32
	Min	1.74	311	0.03	10	3	1
	Median	3.05	590	0.15	10	5	4
	Max	6.56	1029	0.30	60	7	6

* -- For variables marked † Mean is geometric mean, and Standard Deviation (Std) is CV(%)

Figure 1. Mean PK Profiles

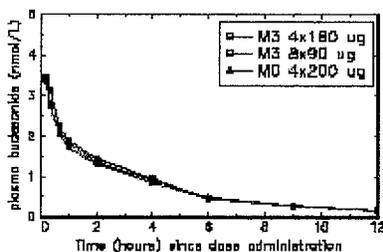


Table 2. Relative Bioavailability (Study # 0601)

Treatment ratios	AUC		C _{max}	
	Ratio (%)	90% CI	Ratio (%)	90% CI
M3 4 x 180 µg/M0 4 x 200 µg	96.3	90.9, 102.1	100.4	92.1, 109.4
M3 4 x 180 µg/M3 8 x 90 µg	92.2	87.0, 97.7	94.4	86.6, 102.9

Conclusion:

Based on the data from this study the systemic exposure of the two formulations and the dosage strengths are comparable.

Study 0708:

This study was originally submitted in October 1999 as part of the Phase 4 commitment as stated in the approval letter dated June 24, 1997 (NDA 20-441). This Phase 4 commitment was mainly related to CMC issues in order to improve the dose-delivery characterization and spherization process. Based on the data from this study as well as CMC related data, M0-ESP was approved in December 8, 2000.

The study was conducted in 36 healthy subjects following administration 640 mcg (4 x 160 mcg) using M0-ESP and a replicate of 640 mcg (4 x 160 mcg) using M0 device in a 3-way crossover design. The 90% CI for the C_{max} and AUC were within 80 to 125% (Tables 3 and 4).

Table 3. 90% CI for AUC (Study # 708)

Contrast	ratio (%)	90% C. I.	
Modified / mean of Current, replicate I and II	99.45	94.85	104.29
Modified / Current, replicate I	103.18	94.86	106.80
Modified / Current, replicate II	98.74	95.40	104.27
Current, replicate I / Current, replicate II	98.56	93.38	104.02

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Table 4. 90% CI for Cmax (Study # 708)

Comparison	ratio (%)	90% C. I.	
Modified / mean of Current replicates I and II	101.14	94.29	108.47
Modified / Current, replicate I	100.69	92.90	108.14
Modified / Current, replicate II	101.59	93.32	110.11
Current, replicate I / Current, replicate II	100.89	93.16	108.27

Conclusions:

Based on the above data, it can be concluded that the bioavailability of the M0-ESP is similar relative to that of M0 device. Therefore, M0-ESP was approved and has been marketed since December 2000.

Studies 620 (Phase III Clinical Study):

Study Design:

This is a placebo controlled safety and efficacy study using M3 and M0-ESP devices in asthmatic adults. It is parallel group 12 weeks study at a dose of 180 mcg QD or 360 mcg bid of M3 inhaler and 400 mcg BID or 200 mcg QD of M0-ESP. Blood samples for PK analysis were collected from a small subset of subjects on active treatments.

Results:

The total number of subjects who provided viable data ranged from 2 to 13 as shown in **Table 5**. In some instances, only 2 and 3 subjects provided data for AUC_{0-12h} for M3 arms at doses of 360 mcg BID and 180 mcg QD treatments, respectively. In addition, there was a high variability in the data as shown in **Figure 2**. Specifically, there was one outlier that had a significantly higher systemic exposure compared to the other patients at a dose of 400 mcg BID in M0-ESP arm.

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Table 5. Summary of PK AUC Parameters (Study 620)

Parameter	Treatment group/budesonide content				Total (n=40)
	PULMICORT TBH M3 360 µg bid (168 mg/g) (n=13)	PULMICORT TBH M3 360 µg bid (178 mg/g) (n=10)	PULMICORT TBH M3 180 µg qd (168 mg/g) (n=7)	PULMICORT TBH M3 180 µg qd (178 mg/g) (n=10)	
Steady state AUC (nmol*h/L)					
N	12	10	5	10	37
Mean (SD)	5.88 (2.11)	4.87 (2.84)	2.34 (0.59)	2.93 (1.85)	4.33 (2.50)
Range (min-max)	2.6 to 10.0	0.6 to 8.3	1.7 to 3.1	0.9 to 7.2	0.6 to 10.0
AUC ₀₋₂₄ (nmol*h/L)					
N	13	10	6	10	39
Mean (SD)	5.19 (1.92)	3.80 (2.39)	1.54 (0.51)	1.99 (1.36)	3.46 (2.28)
Range (min-max)	2.1 to 8.1	0.5 to 6.7	0.9 to 2.2	0.5 to 5.0	0.5 to 8.1
AUC _{0-12h} (nmol*h/L)					
N	2	10	3	10	25
Mean (SD)	8.87 (1.53)	4.87 (2.84)	2.01 (0.55)	2.58 (1.67)	3.93 (2.79)
Range (min-max)	7.8 to 10.0	0.6 to 8.3	1.5 to 2.6	0.8 to 6.4	0.6 to 10.0

AUC Area under the drug-plasma-concentration-time curve; TBH TURBUHALER.
PULMICORT TURBUHALER M3, new device. PULMICORT TURBUHALER M0-E3P, current device.

Figure 2. Individual Plasma Concentration-Time Profiles (Study 620)

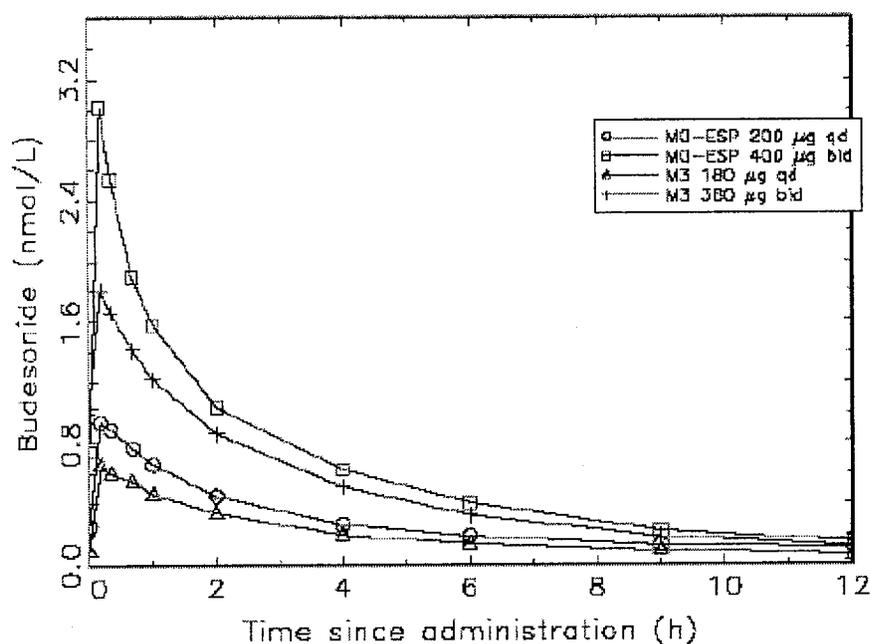
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Reviewer's Comments:

Due to the observed high variability and the small number of subjects at each dose/treatment levels, the mean data and specifically the mean plasma concentration-time profile of budesonide it is very difficult to reach a definitive conclusion (**Figure 3**). However, considering all the variability in the data, the exposure from M3 appears to be lower than M0-ESP. The extent of the clinical impact of this lower exposure on the efficacy of the new inhaler is questionable at this time.

Figure 3. Mean Plasma Concentration-Time Profile for M3 and M0-ESP (Study 620)



Conclusions:

From the PK perspective, the data is inconclusive due to the small number of subjects at each treatment. However, there are no systemic safety issues with M3 device as the systemic exposure appears to be lower than M0-ESP. Therefore, the low systemic exposure with M3 may have some impact on the efficacy.

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Study 726 (Phase 3 Clinical Study):

Study Design:

This study was similar in design to Study 620 in which M3 and M0-ESP devices were tested. The doses administered in each arm of this study are also similar to those administered in study 620. However, the main difference is that the study was conducted in children and adolescents of age ranging from 6 to 17 years.

Results:

As was discussed in study 620, the number of subjects was also small and the variability was also high in order to make a definitive conclusion of the data. In each arm there were approximately 8 subjects with a total of 32 subjects in the four arms. In terms of exposure with M3 inhaler, the data appears to be consistent with study 620 indicating a lower or comparable exposure compared to M0-ESP (**Tables 6 and 7**).

As in study 620, there was a highly variability in the plasma concentration-time profiles (**Figure 4**). Because of the high variability, there was some separation in the mean plasma concentration-time profiles between M3 and M0-ESP (**Figure 5**). These mean profiles are also consistent with those obtained from Study 620 indicating a lower exposure from M3 device compared to M0-ESP.

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Table 6. Statistical Summary of PK Parameters, Geometric Means (Study # 726)

Variable	PULMICORT TURBUHALER treatment	n	GMean	CV	Min	Median	Max
AUC (nmol*h/L)	M0-ESP 200 µg qd	8	1.262	157.5	0.17	1.52	4.61
	M0-ESP 400 µg bid	10	4.752	46.3	2.40	4.93	8.23
	M3 180 µg qd	6	1.746	59.2	0.87	1.52	4.27
	M3 360 µg bid	8	4.143	39.0	2.14	4.24	6.45
Cmax (nmol/L)	M0-ESP 200 µg qd	8	0.381	228.7	0.03	0.39	2.22
	M0-ESP 400 µg bid	10	1.898	41.4	0.78	2.06	2.86
	M3 180 µg qd	6	0.444	66.2	0.16	0.52	0.89
	M3 360 µg bid	8	1.519	46.3	0.85	1.34	2.74
T1/2 (h)	M0-ESP 200 µg qd	8	3.32	22.5	2.7	3.3	5.1
	M0-ESP 400 µg bid	10	3.81	37.2	1.9	4.0	7.3
	M3 180 µg qd	6	3.48	38.3	2.3	3.1	6.8
	M3 360 µg bid	8	3.68	19.1	3.0	3.4	4.8
AUC _{0-5h} (nmol*h/L)	M0-ESP 200 µg qd	8	0.944	179.0	0.10	1.08	3.59
	M0-ESP 400 µg bid	10	3.796	50.2	1.89	3.80	6.56
	M3 180 µg qd	6	1.281	63.5	0.58	1.09	3.23
	M3 360 µg bid	8	3.267	39.5	1.71	3.33	4.94
AUC _{0-12h} (nmol*h/L)	M0-ESP 200 µg qd	7	1.581	102.1	0.43	1.45	4.37
	M0-ESP 400 µg bid	9	4.546	46.6	2.40	4.15	8.23
	M3 180 µg qd	6	1.598	62.2	0.78	1.34	4.10
	M3 360 µg bid	7	4.553	29.2	3.24	4.93	6.45

bid Twice daily. qd Once daily.

PULMICORT TURBUHALER M3, new device. PULMICORT TURBUHALER M0-ESP, current device.

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Table 7. Relative Systemic Exposure from M3 and M0-ESP (Study # 726)

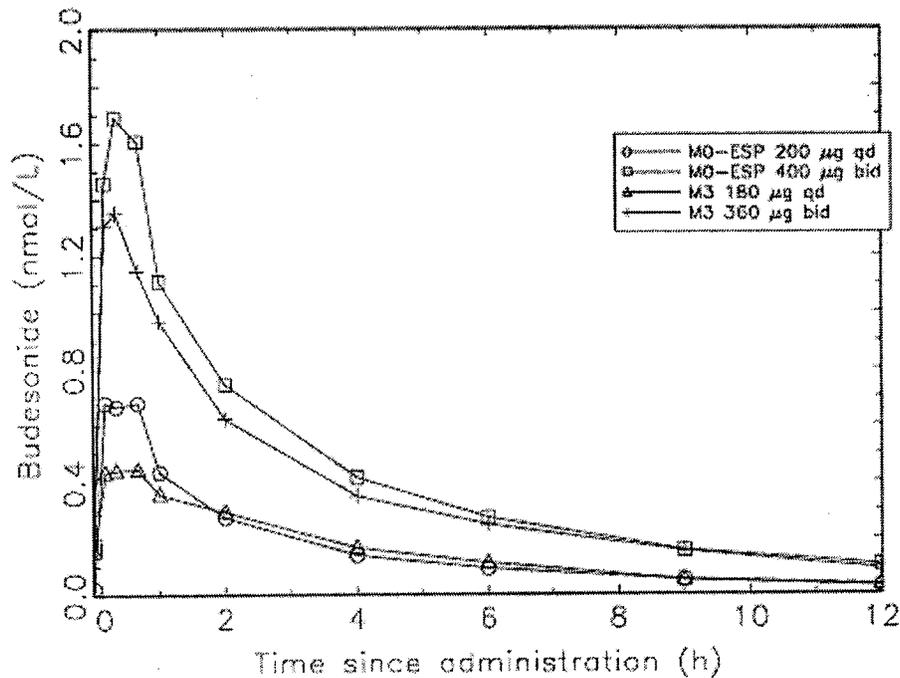
Variable	PULMICORT TURBUHALER treatment contrast	Mean ratio	90% CL
AUC	M3 180 µg qd vs. M0-ESP 200 µg qd	138.3	(74.0 to 258.4)
	M3 360 µg bid vs. M0-ESP 400 µg bid	87.2	(50.3 to 151.0)
C _{max}	M3 180 µg qd vs. M0-ESP 200 µg qd	116.7	(56.5 to 240.8)
	M3 360 µg bid vs. M0-ESP 400 µg bid	80.0	(42.4 to 151.2)
AUC _{0-5h}	M3 180 µg qd vs. M0-ESP 200 µg qd	135.7	(69.6 to 264.5)
	M3 360 µg bid vs. M0-ESP 400 µg bid	86.1	(47.9 to 154.7)
AUC _{0-12h}	M3 180 µg qd vs. M0-ESP 200 µg qd	101.1	(59.1 to 172.9)
	M3 360 µg bid vs. M0-ESP 400 µg bid	100.2	(61.6 to 162.9)

bid Twice daily. qd Once daily. CL Confidence limit.

Figure 4. Individual Plasma concentration Time-Profiles (Study # 726)

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Figure 5. Mean Plasma Concentration-Time Profiles (Study # 726)



Reviewer's Comments (Studies 620 and 726):

The PK data from studies 620 and 726 is limited due to the small number of subjects with good data in each treatment arm (n=2 to 8). Also, these are not crossover studies. The following are some of the specific issues:

- Only 2 subjects provided AUC₀₋₁₂ data in one of the arms in study # 620.
- There were some outliers in both studies. Specifically, in study 620 one subject had significantly higher systemic exposure. The high variability along with some of the outliers affected the overall mean data.

From the PK perspective and considering all sources of variability, M3 and M0-ESP produce comparable exposure. However, the exposure from M3 could be lower than M0-ESP. Therefore, there is no systemic safety concern. In addition, the 90% CI for PK parameters from study 601 and 708 are within the 80 to 125% for M3 and M0.

However, the data from the subsets of patients in clinical Studies 620 and 726 can not be ignored. The clinical data should be interpreted with the variability in mind. However, in terms of systemic exposure and comparability, the emphasis should be on study 601. The situation can be simplified as follows:

Study (708): A (M0) = B (M0-SEP)
 Study (601): C (M3) = A (M0)
 Study (620 and 726) = C ≠ B (?)

In conclusion, the PK data should be carefully integrated with clinical data efficacy to assess the overall performance of the M3 device.

Comparative Analysis Across Studies (#0601 and 0708):

The objective of this analysis is to determine the comparative bioavailability link between M3 (180 mcg per inhalation) and M0-ESP. Studies 601 and 708 were conducted to establish the relative bioavailability between the following inhalers:

Study 601: M3 vs M0
 Study 708: M0 vs M0-ESP

No formal PK study was conducted to establish the link between M3 (the --to-be marketed version) and M0-ESP (the currently marketed version). The only PK data that is available to establish the link between M3 and M0-ESP is from the subsets of patients in Phase 3 Studies, 620 and 726. As described above, the usefulness of this data is limited and can not be used to provide definitive conclusions.

Therefore, the sponsor conducted across study comparative analysis for the data from study 601 and 708 using ANOVA. Due to several sources of variability including but not limited to different population (patients vs. healthy) the exposure from M0 were different between the two studies. Therefore, the sponsor corrected the values of M3 and M0-ESP based on M0 exposure. This was performed by simply dividing each subject's value from M3 or M0-ESP by the corresponding value from M0 in each study.

Results:

Based on this analysis, the 90% CIs for ratio of Cmax and AUC were within 80 to 125% for M0, M3, and M0-ESP (Table 8). Considering the variability in the data, the exposure from the two devices appears to be comparable as shown in Figure 6. Based on this analysis, the exposure in asthmatic subjects appears to be approximately 15% (13% to 16%) lower than in healthy subjects (Table 9).

Table 8. Bioequivalence Tests Between M3 (Study 601) and M0-ESP (Study 708)

Parameter	M3/M0	M0-ESP/M0	M3/M0-ESP	90% confidence limits
AUC _{0-12h} (%)	96.54	99.46	97.07	(89.74 to 105.00)
C _{max} (%)	101.01	101.06	99.95	(88.05 to 113.47)

Figure 6. Individual AUC and Cmax Values of Budesonide for M3 and M0-ESP Expressed as Percent of Corresponding Parameter After Administration of Budesonide via M0

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Table 9. Statistical Analysis Between Astmatic Subjects (Study 601) and Healthy Subjects (Study 708) for M0 Inhaler.

Parameter	Asthma	Healthy	Asthma/Healthy (%)	90% CI
AUC _{0-12h} (nmol*min/L)	537.7	615.2	87.41	(79.50 to 96.11)
C _{max} (µmol/L)	3.28	3.91	83.94	(73.77 to 95.52)

Conclusions:

From this analysis it can fairly be stated that overall, M3 and M0-ESP devices produce a comparable systemic exposure to budesonide.

Pop PK Analysis:

This analysis covers pooled PK data collected from three different inhalers, M0 200 mcg, MO-ESP 200 mcg, and M3 (90 and 180 mcg). The main object of this analysis is to provide additional support to link M3 and MO-ESP and to examine the effects of covariate on the PK of budesonide.

The focus of this analysis was on the effect of covariates on the apparent clearance (Cl/F) and the apparent steady-state volume of distribution (Vss/F). Several covariates were used in this analysis including but not limited to: weight, age, race, and body mass index (BMI). A total of 365 subjects were included in the analysis obtained from 11 current and old studies reported throughout the pulmicort development program. The subjects demographics for these studies are as follows:

- 4 studies in healthy subjects
- 7 studies in asthmatic patients
- 2 studies in pediatrics ages 6 to 11 years of age
- 2 studies in adolescents 12 to 17 years of age

Results:

- The results of the Pop PK analysis are summarized in **Tables 10 and 11 and Figures 6-9**.
- The apparent (Cl/F) was influenced to some degree by age, weight, height, BMI, CrCl, and race. Also, the apparent volume of distribution (V_{ss}/F) was influenced by inhaler type, age, weight, and height (**Figures 6-9**).

Table 10. Summary of Pop PK Analysis of PK Parameters by Inhaler

	M0 SD n=165	M0-ESP SD n=112	M3 SD n=96	M0 SS n=33	M0-ESP SS n=62	M3 SS n=53	All n=541
Cl/F (L/h) (range)	191.7 94-1257	213.4 108-2259	191.1 118-353	183.3 43-508	182.3 27-4099	205.9 64-1542	195.3 27-4099
V _{ss} /F (L) (range)	751.6 328-9599	832.1 351-8706	835.0 474-2181	765.5 238-2451	865.9 111-39941	972.6 331-6946	820.4 111-39941

SD single dose; SS steady state; Cl/F apparent clearance; V_{ss}/F volume of distribution (steady state)

- The systemic exposure from M0 was slightly higher than M0-ESP. In addition, consistent with the data from other studies, the systemic exposure from M3 was slightly lower than M0-ESP (**Table 11 and Figure 6**).

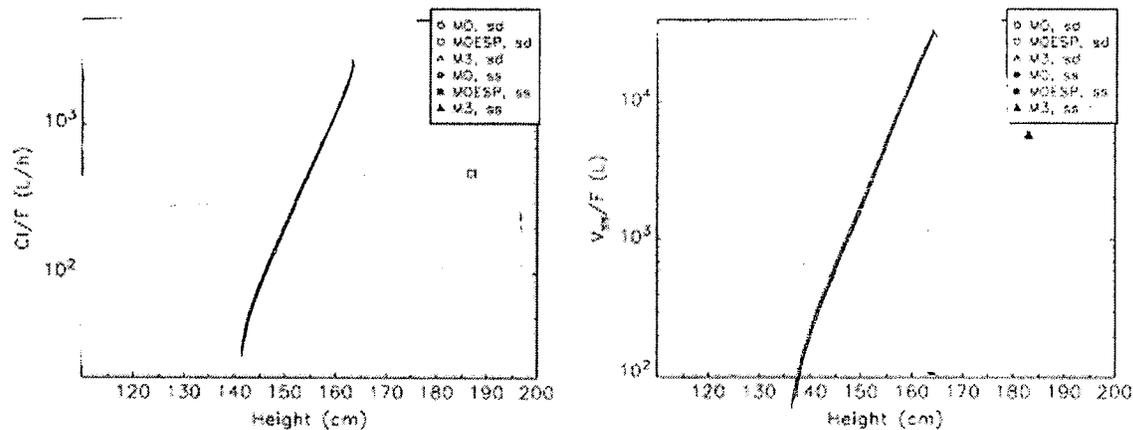
Table 11. Summary of PK Parameters from the Pop PK Analysis

Parameter	Estimate	95% CI	CV%
Cl/F (L/h)	188.1	(176.8, 200.1)	53.4
V ₂ /F (L)	33.1	(30.7, 35.6)	307.3
V ₃ /F (L)	540.1	(492.2, 592.7)	115.4
Q (L/h)	84.2	(77.6, 91.3)	106.9
<i>a</i>	0.38	(0.37, 0.40)	-
F _{rel} (M0/M0-ESP)	1.12	(1.03, 1.21)	-
F _{rel} (M3/M0-ESP)	1.00	(0.92, 1.08)	-

a first-order absorption rate; F_{rel} relative bioavailability

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Figure 9. Effect of Height on Apparent Clearance (Cl/F) and Volume of Distribution (V_{ss}/F)



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Conclusions:

Based on this analysis, it can be concluded that considering all the variability in the data among all studies, the systemic exposure to budesonide is overall comparable among the three inhaler versions (M0, M0-ESP, and M3). The data is also in good agreement with the conclusions drawn from a cross-study comparison between Studies 708 and 601.

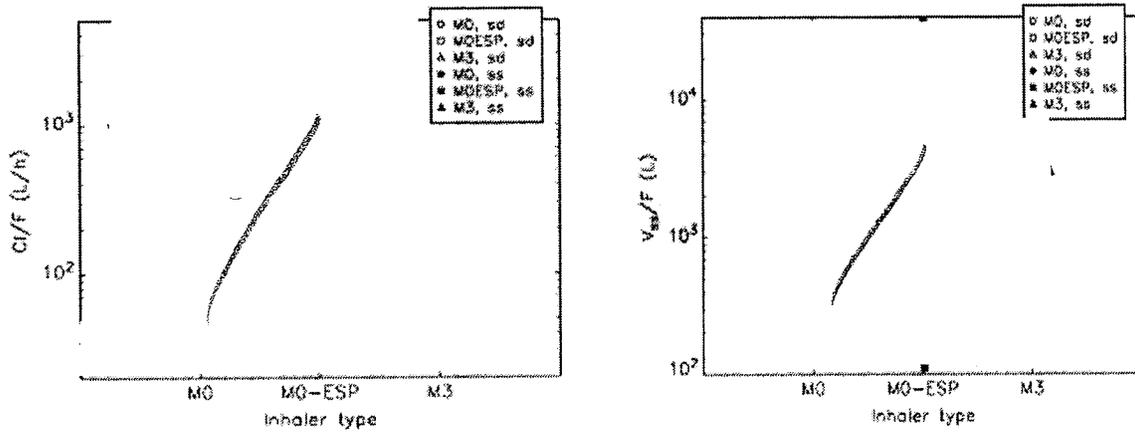
In terms of the effect of covariates on the apparent clearance and volume of distribution the analysis shows some but inconsistent effect. Although, some of these effects are at statistical significant level, the clinical impact of these small effects could be questionable.

Labeling Comments:

The labeling comments will be incorporated directly into the sponsor's proposed label after the discussion with the review team

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Figure 6. Figure . Effect of Inhaler Type on Apparent Clearance (Cl/F) and Volume of Distribution (Vss/F) (Exposure from M0-, M0-ESP, and M3)



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Figure 7. Effect of Age on Apparent Clearance (Cl/F) and Volume of Distribution (Vss/F)

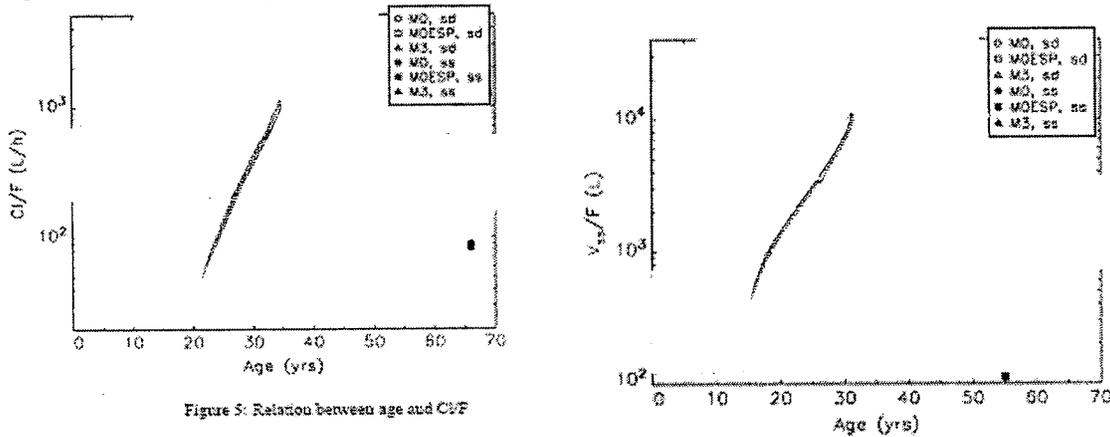
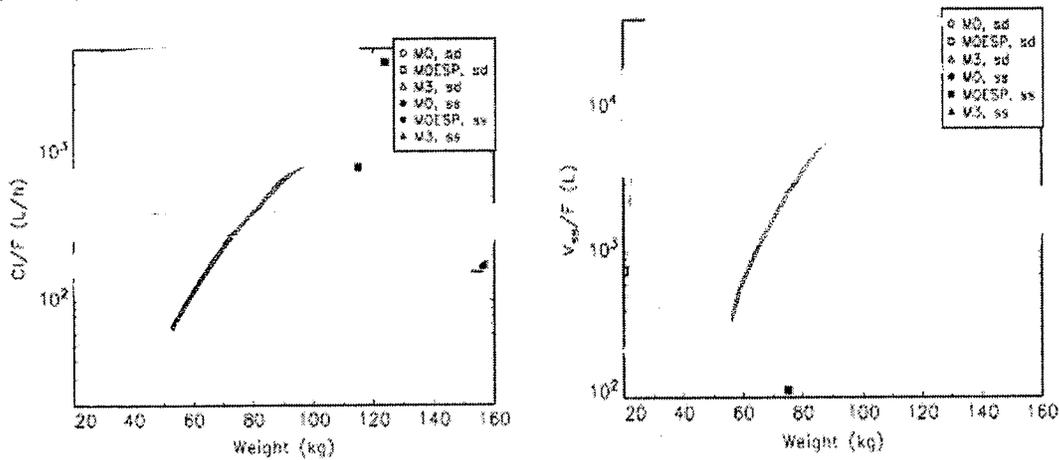


Figure 5: Relation between age and Cl/F

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Figure 8. Effect of Weight on Apparent Clearance (Cl/F) and Volume of Distribution (Vss/F)



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27 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

✓ Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Sayed Al-Habet
5/18/2006 05:46:42 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
5/19/2006 08:43:28 AM
BIOPHARMACEUTICS
I concur

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Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission				
	Information		Information	
NDA Number	21-949	Brand Name	PULMICORT TURBUHALER®	
OCPB Division I	HFD-870	Generic Name	Budesonide	
Medical Division	HFD-570	Drug Class	Anti-asthmatic	
OCPB Reviewer	Sayed (Sam) Al Habet, R.Ph., Ph.D.	Indication(s)	Asthma	
OCPB Team Leader	Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.	Dosage Form: MDI (Metered Dose Inhaler)	Inhalation Powder	
		Dosing Regimen	As Needed (BID-TID)	
Date of Submission	September 12, 2005	Route of Administration	Oral Inhalation	
Estimated Due Date of OCPB Review	May 12, 2006	Sponsor	AstraZeneca	
PDUFA Due Date	July 12, 2006	Priority Classification	S	
Division Due Date	June 12, 2006			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	X	2		
multiple dose:	X			
Patients-				
single dose:		2		
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				

Phase 3 clinical trial:			
Population Analyses -			
Data rich:			
Data sparse:			
II. Biopharmaceutics			
Absolute bioavailability:			
Relative bioavailability -			
solution as reference:			
alternate formulation as reference:		2	
Bioequivalence studies -			
traditional design; single / multi dose:	X	2	
replicate design; single / multi dose:			
Food-drug interaction studies:			
Dissolution:			
(IVIVC):			
Bio-wavier request based on BCS			
BCS class			
III. Other CPB Studies			
Genotype/phenotype studies:			
Chronopharmacokinetics			
Pediatric development plan			
Literature References			
Total Number of Studies			
Filability and QBR comments			
	"X" if yes	Comments	
Application filable ?	Yes	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?	
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.	
QBR questions (key issues to be considered)			
Other comments or information not included above			
Primary reviewer Signature and Date	Sayed (Sam) Al Habet, R.Ph., Ph.D.		
Secondary reviewer Signature and Date	Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.		

CC: NDA HFD-570, HFD-870 (Al Habet, Fadiran, Malinowski), CDR (B. Murphy, biopharm file)

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/s/

Sayed Al-Habet
11/3/2005 02:53:01 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
11/4/2005 02:49:45 PM
BIOPHARMACEUTICS
I concur

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCES
OFFICE OF BIostatISTICS

Filing Review

NDA: 21,949
Drug Name : Pulmicort Turbuhaler M3
Indication: Asthma
Applicant: AstraZeneca
Dates: Electronic submission dated 09/12/2005
Biometrics Division: Division of Biometrics II (HFD-715)
Statistical reviewers: James Gebert, Ph.D.
Concurring Reviewer: Ruthanna C. Davi, M.S., Statistics Team Leader
Medical Division: Division of Allergy and Pulmonary Drug Products
(HFD-570)
Clinical reviewer: J. Kaiser, M.D.
Medical Team Leader: P. Starke, M.D.
Project manager: C. Jackson
Keywords: Clinical studies

The statistical review of this submission will focus on two studies, SD-004-0620 and SD-004-0726. On their face, these studies have the potential to support the described indication. The corresponding electronic data files are accessible. Therefore, the submission is adequate for filing from a statistical perspective. This reviewer has the following information request from the sponsor.

Information request

The values of the variables CONTENT and _CONTENT in files _PULM02 and _DIARY02 in folder SD-004-0620 do not match for all subjects. Explain. Specify the correct values for CONTENT and _CONTENT in file _PULM02 in folder SD-004-0620 for patients 4007, 4009, 4010, 4011, 4030, 4041, 4043, 4044, and 4053.

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/s/

James Gebert
10/27/2005 03:18:20 PM
BIOMETRICS

Ruth Davi
10/27/2005 03:32:26 PM
BIOMETRICS

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