



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL MEMORANDUM

Additional Statistical Analyses of Human Factor Study

NDA Number: 205920
Submission date: 06/28/2016
Drug Name: [REDACTED] ^{(b) (4)} 125 mcg/inhalation
Biometrics Division: Division of Biometrics VII, Office of Biostatistics
Statistical Reviewer: Rima Izem, Ph.D. (Team Leader)
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Background for this memorandum: this memorandum summarizes for the record some analyses the statistical reviewer conducted for the human factor study in NDA 205920 submitted in 06/28/2016. In December 2nd 2016, reviewers from Division of Medication Error Prevention and Analysis (DMEPA) at FDA re-adjudicated the outcomes in the human factor study. The primary statistical review archived in DARRTS on December 7th 2016 used the sponsor adjudication rather than the re-adjudicated outcomes and did not include the additional analyses in this memorandum. We refer to the summary of human factor study and analyses with sponsor adjudication in primary statistical review. We refer to the completed safety review by Grace Jones in DMEPA for summary of study design and motivation for the re-adjudication.

Statistical analyses:

Table 1 presents the success rate and 95% confidence interval for the first three tasks of the human factor study based on the re-adjudicated data by DMEPA shown in Appendix A.

Results on sponsor’s adjudication, previously reported in the statistical review, are presented in Appendix A for comparison purposes. More granular count results for the re-adjudicated data broken down by each task are shown in Appendix B and Appendix C.

Table 1: Success Rates for Each Task and for All Tasks in Human Factor Study

Tasks	DMEPA Re-Adjudicated Success Rates	95% Confidence Interval¹
Task 1: First Use	131/151 (87%)	(80%, 92%)
Task 2: Cleaning	133/151 (88%)	(82%, 93%)
Task 3: Routine use	132/151 (87%)	(81%, 92%)
All three tasks ²	106/151 (70%)	(62%, 77%)

1. Confidence interval use Clopper-Pearson exact method
2. This is a composite endpoint for success on all three tasks. That is, a subject is deemed successful if he completed each of three tasks correctly based on the re-adjudication.

Appendix A: Sponsor Adjudication Results

This Table is a subset of results reported in Table 22 of Yueqin Zhao’s statistical review (archived in DARRTS on 12/7/2016). This table shows the results for the Applicant’s definition of success and a stricter definition of success. The applicant counted as successes those who had completed the task (C) or those who completed with issues (CI). The stricter definition only count those who completed the task (C) as successes.

CBT/ALHFQ	Risk-Based Evaluation Dataset (N=151)				
	C	CI	NC	Applicant's definition (success as C or CI) (95% CI)	Stricter definition (success as C only) (95% CI)
Critical Behavioral Tasks					
Task 1: First Use*	105	38	8	95% (90%, 98%)	70% (62%, 77%)
Task 2: Cleaning	91	56	4	97% (93%, 99%)	60% (52%, 68%)
Task 3: Routine Use	128	21	2	99% (95%, 100%)	85% (78%, 90%)

Appendix B: DMEPA re-adjudication

Sponsor and DMEPA re-adjudicated dataset. Here is a documentation of each variable in this dataset

- Pid is the patient id as coded by the sponsor
- Task 1 to task 3 are the sponsor adjudicated results for each task with C for completed, CI for completed with issues and NC for not completed.
- Task1.DMEPA to Task3.DEMPA are the DMEPA re-adjudicated results for each task with C for completed and F for failed to complete.

	pid (b)(6)	task1	task2	task3	Task1.DMEPA	Task2.DMEPA	Task3.DMEPA
1		C	CI	C	C	A	C
		CI	C	C	A	C	C
		CI	CI	C	F	F	C
		C	C	C	C	C	C
		C	C	C	C	C	C
		C	C	C	C	C	C
		C	C	C	C	C	C
		CI	C	C	A	C	C
		C	C	C	C	C	C
10		NC	C	C	F	C	C
11		C	C	C	C	C	C
12		C	C	C	C	C	C
13		CI	C	C	A	C	C
14		C	C	C	C	C	C
15		C	CI	C	C	A	C
16		NC	C	C	F	C	C
17		CI	CI	CI	A	A	F
18		C	C	C	C	C	C
19		C	C	C	C	C	C
20		C	C	C	C	C	C
21		C	C	C	C	C	C
22		NC	CI	C	F	A	C
23		C	C	C	C	C	C
24		C	C	C	C	C	C
25		C	CI	C	C	A	C
26		C	C	C	C	C	C
27		C	C	C	C	C	C
28		C	CI	C	C	A	C
29		CI	C	C	A	C	C
30		C	CI	C	C	A	C
31		C	C	C	C	C	C
32		CI	CI	C	A	A	C
33		C	CI	CI	C	A	F

(b) (6)

34	C	C	C	C	C	C
35	NC	CI	C	F	F	C
36	C	CI	C	C	F	C
37	NC	C	C	F	C	C
38	CI	CI	C	A	F	C
39	CI	C	C	A	C	C
40	C	C	C	C	C	C
41	C	C	C	C	C	C
42	C	C	C	C	C	C
43	CI	CI	C	F	A	C
44	C	CI	C	C	A	C
45	C	C	C	C	C	C
46	C	C	C	C	C	C
47	C	C	C	C	C	C
48	C	C	C	C	C	C
49	C	C	C	C	C	C
50	CI	C	C	A	C	C
51	C	CI	CI	C	A	A
52	C	CI	C	C	A	C
53	C	CI	C	C	F	C
54	CI	CI	C	A	F	C
55	C	C	C	C	C	C
56	CI	C	CI	A	C	F
57	CI	C	CI	F	C	F
58	C	CI	C	C	A	C
59	C	C	C	C	C	C
60	CI	C	C	A	C	C
61	C	C	C	C	C	C
62	C	C	C	C	C	C
63	C	C	C	C	C	C
64	CI	CI	C	A	A	C
65	C	CI	C	C	A	C
66	C	C	C	C	C	C
67	CI	C	CI	F	C	F
68	C	C	C	C	C	C
69	C	CI	C	C	A	C
70	CI	CI	C	A	F	C
71	C	CI	C	C	A	C
72	C	CI	CI	C	F	A
73	CI	C	C	A	C	C
74	C	C	C	C	C	C
75	CI	NC	C	F	F	C
76	C	C	C	C	C	C

77	(b) (6)	CI	CI	C	A	A	C
78		C	C	C	C	C	C
79		C	C	CI	C	C	A
80		CI	C	C	A	C	C
81		CI	C	C	A	C	C
82		CI	C	CI	F	C	A
83		CI	C	C	F	C	C
84		C	CI	C	C	A	C
85		C	CI	C	C	F	C
86		C	C	C	C	C	C
87		C	CI	CI	C	A	F
88		CI	C	C	A	C	C
89		C	CI	C	C	A	C
90		C	CI	C	C	A	C
91		C	CI	C	C	A	C
92		C	C	C	C	C	C
93		C	C	C	C	C	C
94		CI	CI	C	A	A	C
95		C	C	C	C	C	C
96		C	CI	C	C	A	C
97		C	C	CI	C	C	F
98		CI	C	C	F	C	C
99		C	C	C	C	C	C
100		C	CI	C	C	A	C
101		C	CI	C	C	A	C
102		C	CI	C	C	A	C
103		C	CI	C	C	A	C
104		C	C	CI	C	C	F
105		CI	CI	C	F	A	C
106		NC	C	CI	F	C	F
107		NC	CI	NC	F	A	F
108		CI	C	CI	A	C	F
109		C	C	C	C	C	C
110		C	C	C	C	C	C
111		C	CI	C	C	A	C
112		CI	CI	C	A	F	C
113		C	C	C	C	C	C
114		CI	C	C	F	C	C
115		C	CI	C	C	A	C
116		C	C	C	C	C	C
117		C	CI	C	C	F	C
118		C	CI	C	C	A	C
119		C	C	CI	C	C	F

(b) (6)

120	C	C	C	C	C	C
121	C	C	C	C	C	C
122	C	C	C	C	C	C
123	C	C	C	C	C	C
124	C	C	CI	C	C	F
125	C	C	C	C	C	C
126	C	CI	C	C	A	C
127	C	CI	C	C	F	C
128	C	C	C	C	C	C
129	CI	C	CI	A	C	F
130	C	C	CI	C	C	F
131	CI	NC	CI	F	F	F
132	C	C	C	C	C	C
133	C	C	C	C	C	C
134	C	CI	CI	C	F	F
135	CI	C	C	A	C	C
136	C	C	C	C	C	C
137	C	C	CI	C	C	F
138	C	C	C	C	C	C
139	C	CI	C	C	A	C
140	C	CI	C	C	A	C
141	CI	CI	C	A	A	C
142	C	C	C	C	C	C
143	C	C	C	C	C	C
144	C	C	C	C	C	C
145	C	CI	C	C	F	C
146	C	CI	C	C	A	C
147	NC	CI	C	F	A	C
148	C	C	C	C	C	C
149	C	NC	NC	C	F	F
150	CI	NC	C	F	F	C
151	CI	CI	C	A	A	C

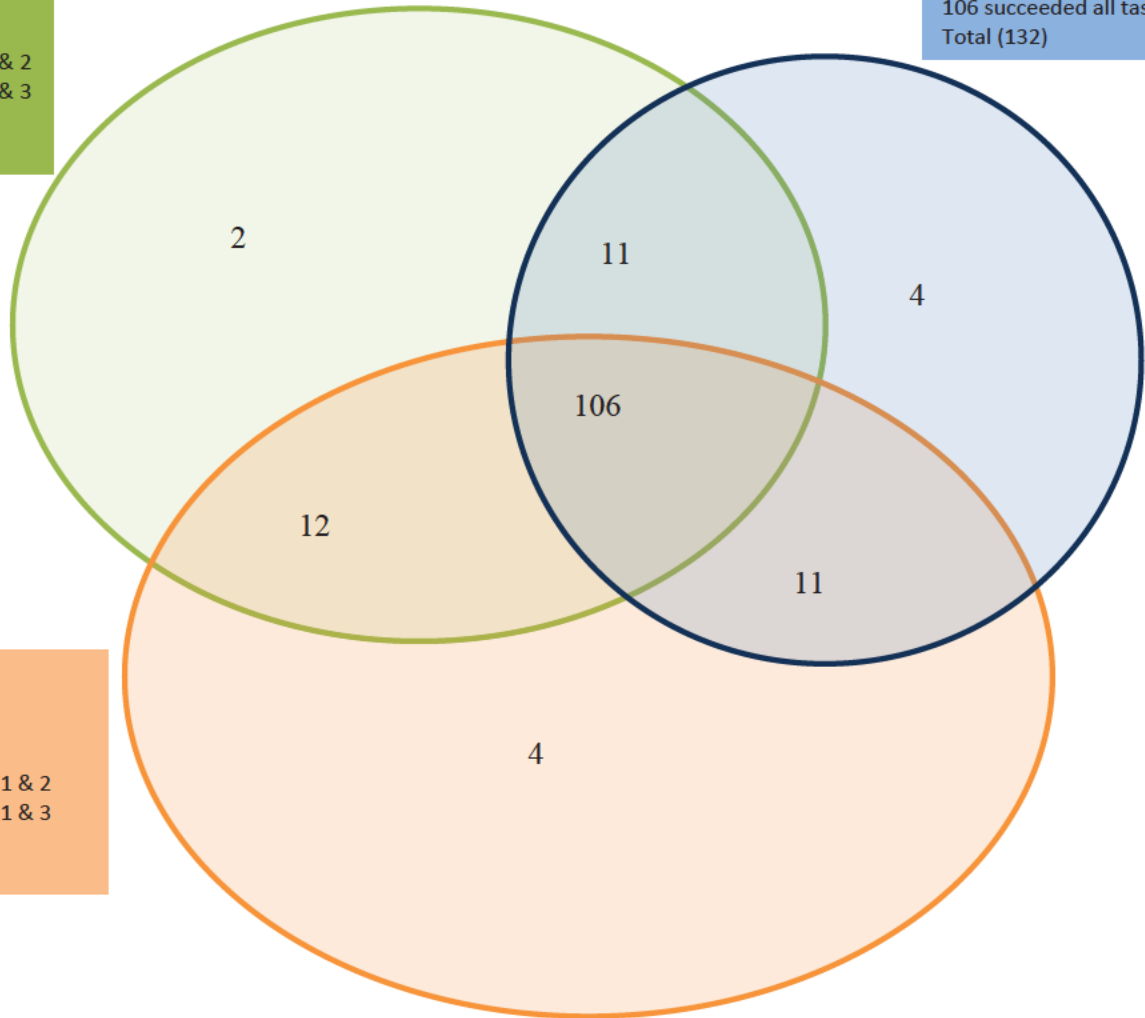
Appendix C: Venn Diagram for Successes (DMEPA Re-adjudication)

**Task 1
First Use**

2 succeed only task 1
 12 succeeded only tasks 1 & 2
 11 succeeded only tasks 1 & 3
 106 succeeded all tasks
 Total (131)

**Task 3
Routine Use**

4 succeed only task 3
 11 succeeded only tasks 1 & 3
 11 succeeded only tasks 2 & 3
 106 succeeded all tasks
 Total (132)



**Task 2
Cleaning**

4 succeed only task 2
 12 succeeded only tasks 1 & 2
 11 succeeded only tasks 1 & 3
 106 succeeded all tasks
 Total (133)

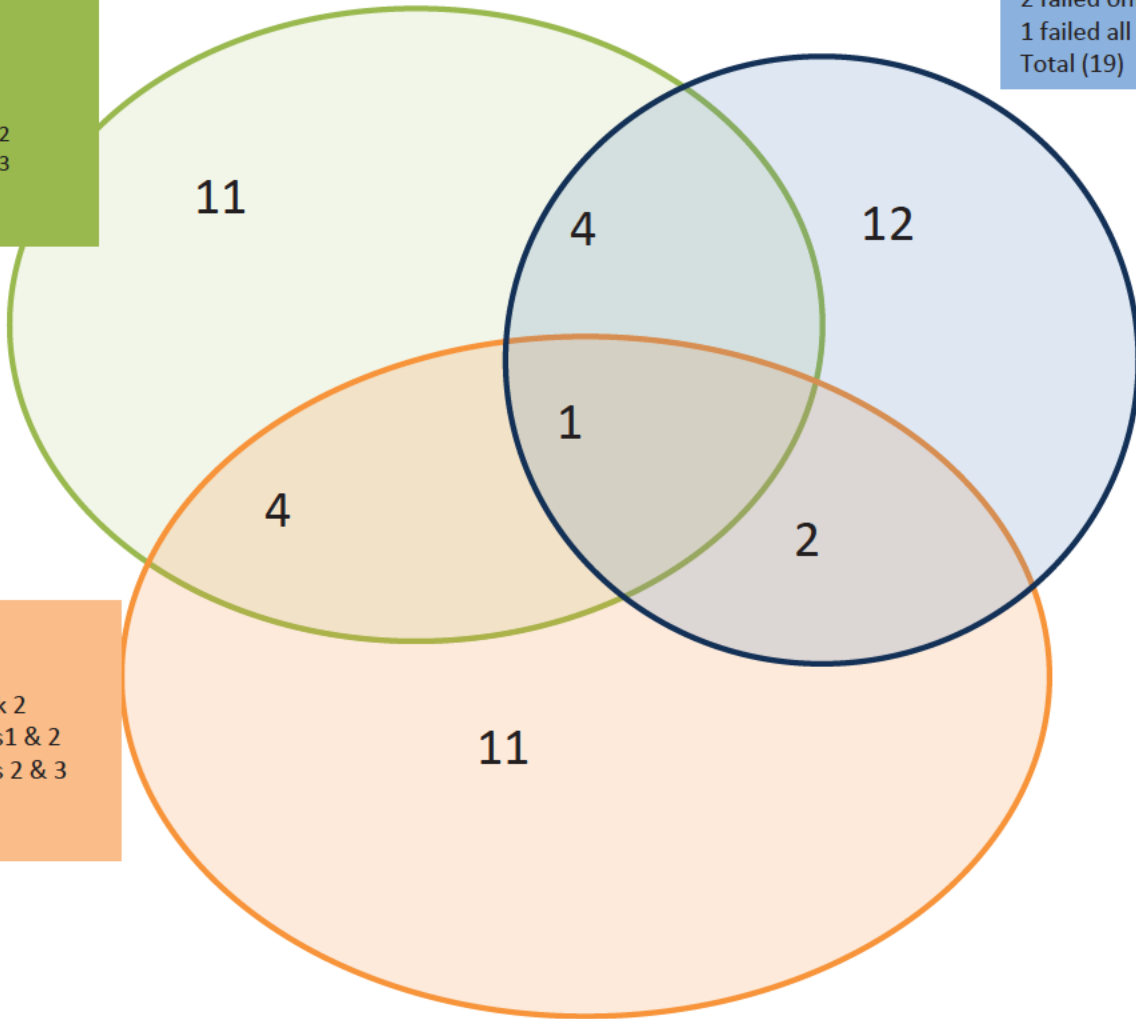
Total Success Rate
 (% subjects who of succeeded in all three tasks)
 106/151 (70%)

Appendix D:
Venn Diagram for failure (DMEPA Re-adjudication)

**Task 1
First Use**
11 failed only task 1
4 failed only tasks 1 & 2
4 failed only tasks 1 & 3
1 failed all tasks
Total (20)

**Task 3
Routine Use**
12 failed only task 3
4 failed only tasks 1 & 3
2 failed only tasks 2 & 3
1 failed all tasks
Total (19)

**Task 2
Cleaning**
11 failed only task 2
4 failed only tasks 1 & 2
2 failed only tasks 2 & 3
1 failed all tasks
Total (18)



Total Failure Rate
(% subjects who of failed at least one task)
45/151 (30%)

Participant ID for those who failed one task:

- Task 1 only: [redacted] (b) (6)
- Task 2 only: [redacted] (b) (6)
- Task 3 only: [redacted] (b) (6)

Participant ID for those who failed multiple tasks:

- Task 1 and task 2: [redacted] (b) (6)
- Task 1 and task 3: [redacted]
- Task 2 and Task 3: [redacted]
- All tasks: [redacted] (b) (6)

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/s/

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12/21/2016

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12/21/2016