DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 27, 2002

To: Robin Conrad, Program Director
Drug Regulatory Affairs
Hoffman-La Roche, Inc.

From: Virginia L. Yoerg, Regulatory Health Project Manager, HFD-530

Through: Stephen P. Miller, Ph.D., Chemistry Team Leader, HFD-530
Rao Kambhampati, Ph.D., Chemistry Reviewer, HFD-530

NDA: 21-481

Drug: Fuzeon (enfuvirtide) for Injection

Subject: Chemistry comments regarding labeling

The following comments and recommendations are being conveyed on behalf of Rao Kambhampati, Ph.D., regarding the proposed labeling submitted in your amendment to NDA 21-481, dated October 31.

Labels on Commercial Vial and Free Goods Vial:

1. Please change [redacted] to "For SC Use after Reconstitution" and move it to under "Single Use Vial".

2. Please change [redacted] to the following: "Each vial contains 108 mg of enfuvirtide to provide delivery of 90 mg".

All Carton Labels:

3. Please increase the prominence of "(enfuvirtide) for Injection" in the title by changing it to bold type font.

4. Please change [redacted] to "For SC Use after Reconstitution".

5. Please change [redacted] to "Each vial contains 108 mg of enfuvirtide to provide delivery of 90 mg".

Labels on Commercial Carton 30s, Free Goods Carton 30s and Free Goods Kit Carton:

6. Add the following sentence to the Preparation of Solution paragraph: Each 1 mL of the reconstituted solution contains 90 mg of enfuvirtide.

Labels on Commercial Kit Carton, Commercial Carton 60s (Back-up carton), and Free Goods Kit Carton:

7. Please limit the patent and license information and trademark rights information to one side of the carton.

We are providing this information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Virginia L. Yoerg
Regulatory Health Project Manager
Division of Antiviral Drug Products

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

/s/

Virginia Yoerg
11/27/02 03:39:58 PM
CSO

hard copy of fax signed and sent to applicant.

Stephen Paul Miller
12/3/02 11:52:46 AM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: December 18, 2002

To: Robin Conrad, Program Director
Drug Regulatory Affairs
Hoffman-La Roche, Inc.

From: Virginia L. Yoerg, Regulatory Health Project Manager, HFD-530

Through: Tom Hammerstom, Ph.D., Statistics Reviewer, HFD-530
Greg Soon, Ph.D., Statistics Team Leader, HFD-530
Melisse Baylor, M.D., Medical Officer, HFD-530
Steven Gitterman, M.D., Medical Team Leader, HFD-530

NDA: 21-481

Drug: Fuzeon (enfuvirtide) for Injection

Subject: Statistical comments regarding T20-301 and T20-302

The following comments are being conveyed on behalf of Tom Hammerstrom, Ph.D., regarding your statistical analyses for protocols T20-301/NV16504 and T20-302/BV16052.

Upon reflection, we have decided that subjects who first become BLQ after week 24 (day 197) will be counted as failures in the label so that the curve of percent BLQ will go up and then down. This curve won't be in the label since this wasn't the primary endpoint but the value of the curve at day 197 will be included.

The attached text gives the complete listing for all subjects with which we still disagree. In the listing BLQDAY and VFDAY are explained above, BLQ = running total of consecutive visits with LOGHIV <= 1.6902, up to a maximum of 2, REBOUND = 0 until BLQ = 2, then it is a running total of consecutive visits with LOGHIV > 1.6902, TFDAY is the running calculation of day of viral failure, VFDAY = final value for day of viral failure is the maximum of TFDAY, VFAIL = 0 if never failed, 1 if failed. TRT2SD = day of switch.

TRIAL_302

TRT	BLQDAY	VFDAY	PT
1	99	344	2062
1	172	211	7158
2	29	225	3276
2	43	96	2041
2	57	141	1190
2	57	393	6121
2	59	286	7032
2	59	337	7273
2	85	224	3062
2	92	106	4098
2	93	226	5152
2	98	287	1092
2	99	266	1093
2	100	335	6092
2	101	288	7183
2	113	225	5181
2	162	219	6138
2	162	225	1032
2	163	224	6431
2	166	225	3477
2	169	225	7017
2	169	337	2064
2	170	225	3275
2	170	288	5211

TRIAL_302

TRT=1 BLQDAY=99 VFDAY=344 Patient=2062 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.56	0	0	1	0
8	3.77	0	0	1	0
15	3.49	0	0	1	0
29	3.20	0	0	1	0
43	2.99	0	0	1	0
57	2.67	0	0	1	0
73	3.31	0	0	1	0
85	2.04	0	0	1	0
99	1.69	1	0	1	0
113	1.69	2	0	113	0
141	1.83	2	1	141	0
169	1.69	2	0	169	0
227	1.69	2	0	227	0
288	1.69	2	0	288	0
344	1.79	2	1	344	0

TRT=1 BLQDAY=172 VFDAY=211 Patient=7158 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.39	0	0	1	0
8	4.64	0	0	1	0
15	4.25	0	0	1	0
32	3.68	0	0	1	0
43	3.73	0	0	1	0
57	3.11	0	0	1	0
67	3.48	0	0	1	0
85	2.41	0	0	1	0
99	3.20	0	0	1	0
113	1.69	1	0	1	0
144	1.76	0	0	1	0
172	1.69	1	0	1	0
211	1.69	2	0	211	0

TRT=2 BLQDAY=29 VFDAY=225 Patient=3276 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.60	0	0	1	0
8	3.06	0	0	1	0
14	2.27	0	0	1	0
29	1.69	1	0	1	0
43	1.69	2	0	43	0
57	1.69	2	0	57	0
71	1.69	2	0	71	0
85	1.69	2	0	85	0
99	1.69	2	0	99	0
113	1.69	2	0	113	0
141	2.01	2	1	141	0
170	1.69	2	0	170	0
225	1.69	2	0	225	0

TRT=2 BLQDAY=43 VFDAY=96 Patient=2041 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL

1	4.21	0	0	1	1
8	2.73	0	0	1	1
15	2.15	0	0	1	1
29	2.18	0	0	1	1
43	1.69	1	0	1	1
57	1.69	2	0	57	1
68	1.69	2	0	68	1
82	1.69	2	0	82	1
96	1.77	2	1	96	1
110	2.02	2	2	96	1
145	1.69	2	2	96	1
166	1.69	2	2	96	1
222	1.83	2	2	96	1

TRT=2 BLQDAY=57 VFDAY=141 Patient=1190 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.11	0	0	1	1
8	2.62	0	0	1	1
15	2.80	0	0	1	1
29	2.19	0	0	1	1
43	1.76	0	0	1	1
57	1.69	1	0	1	1
70	1.69	2	0	70	1
85	2.09	2	1	85	1
99	1.69	2	0	99	1
113	1.69	2	0	113	1
141	1.70	2	1	141	1
169	1.77	2	2	141	1
223	1.69	2	2	141	1

TRT=2 BLQDAY=57 VFDAY=393 Patient=6121 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	3.68	0	0	1	0
8	2.82	0	0	1	0
15	2.70	0	0	1	0
29	1.69	1	0	1	0
43	1.82	0	0	1	0
57	1.69	1	0	1	0
71	1.69	2	0	71	0
85	1.70	2	1	85	0
99	1.69	2	0	99	0
113	1.69	2	0	113	0
142	2.35	2	1	142	0
176	1.69	2	0	176	0
225	1.69	2	0	225	0
290	1.69	2	0	290	0
339	1.69	2	0	339	0
393	1.69	2	0	393	0

TRT=2 BLQDAY=59 VFDAY=286 Patient=7032 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.23	0	0	1	0
8	3.59	0	0	1	0

15	3.06	0	0	1	0
29	2.35	0	0	1	0
38	1.73	0	0	1	0
59	1.69	1	0	1	0
73	1.69	2	0	73	0
86	1.69	2	0	86	0
101	1.69	2	0	101	0
143	1.69	2	0	143	0
225	1.69	2	0	225	0
286	1.69	2	0	286	0

TRT=2 BLQDAY=59 VFDAY=337 Patient=7273 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.76	0	0	1	0
8	3.68	0	0	1	0
17	2.61	0	0	1	0
31	2.20	0	0	1	0
44	1.96	0	0	1	0
59	1.69	1	0	1	0
87	1.69	2	0	87	0
101	1.69	2	0	101	0
113	1.69	2	0	113	0
141	1.69	2	0	141	0
172	1.83	2	1	172	0
231	1.69	2	0	231	0
287	1.69	2	0	287	0
337	2.16	2	1	337	0

TRT=2 BLQDAY=85 VFDAY=224 Patient=3062 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.60	0	0	1	0
7	4.44	0	0	1	0
28	3.40	0	0	1	0
56	1.97	0	0	1	0
70	2.23	0	0	1	0
85	1.69	1	0	1	0
98	1.69	2	0	98	0
112	1.78	2	1	112	0
141	1.69	2	0	141	0
224	1.69	2	0	224	0

TRT=2 BLQDAY=92 VFDAY=106 Patient=4098 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.68	0	0	1	0
9	2.99	0	0	1	0
19	2.39	0	0	1	0
34	2.55	0	0	1	0
49	2.80	0	0	1	0
78	2.80	0	0	1	0
92	1.69	1	0	1	0
106	1.69	2	0	106	0

TRT=2 BLQDAY=93 VFDAY=226 Patient=5152 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL

1	4.04	0	0	1	0
10	2.68	0	0	1	0
17	2.23	0	0	1	0
37	2.09	0	0	1	0
44	1.95	0	0	1	0
60	1.96	0	0	1	0
71	1.96	0	0	1	0
93	1.69	1	0	1	0
101	1.69	2	0	101	0
120	1.69	2	0	120	0
150	1.72	2	1	150	0
170	1.69	2	0	170	0
226	1.69	2	0	226	0

TRT=2 BLQDAY=98 VFDAY=287 Patient=1092 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.08	0	0	1	0
8	3.96	0	0	1	0
15	3.00	0	0	1	0
29	3.22	0	0	1	0
43	2.78	0	0	1	0
57	2.37	0	0	1	0
70	2.37	0	0	1	0
85	1.74	0	0	1	0
98	1.69	1	0	1	0
114	1.69	2	0	114	0
145	1.69	2	0	145	0
177	1.79	2	1	177	0
231	1.69	2	0	231	0
287	2.25	2	1	287	0

TRT=2 BLQDAY=99 VFDAY=266 Patient=1093 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	3.92	0	0	1	0
9	2.61	0	0	1	0
14	2.48	0	0	1	0
28	1.85	0	0	1	0
42	2.36	0	0	1	0
57	1.99	0	0	1	0
70	1.69	1	0	1	0
84	1.81	0	0	1	0
99	1.69	1	0	1	0
109	1.69	2	0	109	0
125	1.69	2	0	125	0
154	1.69	2	0	154	0
210	1.69	2	0	210	0
266	1.69	2	0	266	0

TRT=2 BLQDAY=100 VFDAY=335 Patient=6092 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.41	0	0	1	0
8	4.17	0	0	1	0
15	3.57	0	0	1	0

27	3.04	0	0	1	0
42	3.10	0	0	1	0
57	2.73	0	0	1	0
71	2.53	0	0	1	0
85	2.22	0	0	1	0
100	1.69	1	0	1	0
118	1.69	2	0	118	0
141	1.69	2	0	141	0
174	1.73	2	1	174	0
225	1.69	2	0	225	0
281	1.69	2	0	281	0
335	1.69	2	0	335	0

TRT=2 BLQDAY=101 VFDAY=288 Patient=7183 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.03	0	0	1	0
8	3.26	0	0	1	0
15	2.67	0	0	1	0
31	2.25	0	0	1	0
45	1.69	1	0	1	0
59	1.71	0	0	1	0
73	1.92	0	0	1	0
85	1.78	0	0	1	0
101	1.69	1	0	1	0
115	1.69	2	0	115	0
143	1.97	2	1	143	0
171	1.69	2	0	171	0
227	1.69	2	0	227	0
288	1.69	2	0	288	0

TRT=2 BLQDAY=113 VFDAY=225 Patient=5181 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.42	0	0	1	0
7	3.13	0	0	1	0
15	3.10	0	0	1	0
29	2.76	0	0	1	0
43	4.36	0	0	1	0
57	4.40	0	0	1	0
71	2.82	0	0	1	0
85	2.02	0	0	1	0
99	1.91	0	0	1	0
113	1.69	1	0	1	0
142	1.69	2	0	142	0
169	1.69	2	0	169	0
225	2.26	2	1	225	0
239	3.23	2	2	225	0
281	1.69	2	2	225	0

TRT=2 BLQDAY=162 VFDAY=219 Patient=6138 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.68	0	0	1	0
7	3.73	0	0	1	0
14	3.06	0	0	1	0

29	2.78	0	0	1	0
44	2.91	0	0	1	0
58	2.77	0	0	1	0
72	2.30	0	0	1	0
85	2.24	0	0	1	0
100	2.14	0	0	1	0
114	2.58	0	0	1	0
135	2.15	0	0	1	0
162	1.69	1	0	1	0
219	1.69	2	0	219	0

TRT=2 BLQDAY=162 VFDAY=225 Patient=1032 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
8	3.90	0	0	1	0
14	3.22	0	0	1	0
25	2.92	0	0	1	0
38	3.15	0	0	1	0
52	2.84	0	0	1	0
80	2.33	0	0	1	0
94	2.27	0	0	1	0
109	2.20	0	0	1	0
135	1.88	0	0	1	0
162	1.69	1	0	1	0
225	1.69	2	0	225	0

TRT=2 BLQDAY=163 VFDAY=224 Patient=6431 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.96	0	0	1	0
6	4.20	0	0	1	0
14	3.34	0	0	1	0
28	3.52	0	0	1	0
42	2.66	0	0	1	0
63	2.16	0	0	1	0
70	2.23	0	0	1	0
84	2.05	0	0	1	0
112	1.99	0	0	1	0
140	2.15	0	0	1	0
163	1.69	1	0	1	0
224	1.69	2	0	224	0

TRT=2 BLQDAY=166 VFDAY=225 Patient=3477 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.71	0	0	1	0
12	3.14	0	0	1	0
19	3.29	0	0	1	0
29	3.06	0	0	1	0
43	2.81	0	0	1	0
57	2.52	0	0	1	0
71	2.20	0	0	1	0
90	1.98	0	0	1	0
99	2.05	0	0	1	0
113	2.43	0	0	1	0
148	2.76	0	0	1	0

166	1.69	1	0	1	0
225	1.69	2	0	225	0

TRT=2 BLQDAY=169 VFDAY=225 Patient=7017 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.52	0	0	1	0
8	3.63	0	0	1	0
15	2.78	0	0	1	0
29	2.24	0	0	1	0
43	2.08	0	0	1	0
57	1.81	0	0	1	0
71	2.08	0	0	1	0
85	1.69	1	0	1	0
99	2.67	0	0	1	0
113	1.69	1	0	1	0
141	1.81	0	0	1	0
169	1.69	1	0	1	0
225	1.69	2	0	225	0

TRT=2 BLQDAY=169 VFDAY=337 Patient=2064 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.74	0	0	1	0
8	3.76	0	0	1	0
17	3.32	0	0	1	0
29	2.77	0	0	1	0
43	2.70	0	0	1	0
57	2.30	0	0	1	0
73	1.98	0	0	1	0
85	1.81	0	0	1	0
99	2.15	0	0	1	0
113	1.70	0	0	1	0
141	2.28	0	0	1	0
169	1.69	1	0	1	0
225	1.69	2	0	225	0
281	1.69	2	0	281	0
337	1.79	2	1	337	0

TRT=2 BLQDAY=170 VFDAY=225 Patient=3275 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.26	0	0	1	0
8	4.16	0	0	1	0
14	3.72	0	0	1	0
29	3.06	0	0	1	0
43	2.71	0	0	1	0
57	1.84	0	0	1	0
71	1.90	0	0	1	0
85	1.72	0	0	1	0
99	1.76	0	0	1	0
113	1.81	0	0	1	0
141	1.81	0	0	1	0
170	1.69	1	0	1	0
225	1.69	2	0	225	0

TRT=2 BLQDAY=170 VFDAY=288 Patient=5211 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.97	0	0	1	0
8	3.60	0	0	1	0
16	3.03	0	0	1	0
29	2.90	0	0	1	0
47	2.76	0	0	1	0
57	2.68	0	0	1	0
71	2.91	0	0	1	0
85	2.35	0	0	1	0
99	2.00	0	0	1	0
113	1.79	0	0	1	0
141	1.80	0	0	1	0
170	1.69	1	0	1	0
233	1.69	2	0	233	0
288	2.15	2	1	288	0
330	1.86	2	2	288	0

TRIAL_301

TRT	BLQDAY	VFDAY	PT
1	43	85	1294
1	59	108	1592
1	71	112	1225
1	72	282	1185
1	85	276	1766
1	92	225	1886
1	120	233	1296
1	170	284	1434
2	11	285	1261
2	30	58	1435
2	44	272	1361
2	46	221	1593
2	58	283	1825
2	85	280	1129
2	85	351	1286
2	98	217	1920
2	99	233	1295
2	99	280	1600
2	113	218	1110
2	113	224	1175
2	113	281	1064
2	142	235	1131
2	168	225	1003
2	168	276	1168
2	169	223	1007
2	169	281	1045
2	169	281	1260
2	169	281	1644
2	169	282	1228
2	169	346	1142
2	169	393	1424
2	176	405	1584
2	177	277	1266
2	177	352	1843
2	179	340	1084

TRIAL_301

TRT=1 BLQDAY=43 VFDAY=85 Patient=1294 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.45	0	0	1	1
8	2.48	0	0	1	1
15	1.94	0	0	1	1
28	1.76	0	0	1	1
43	1.69	1	0	1	1
57	1.69	2	0	57	1
71	1.69	2	0	71	1
85	1.81	2	1	85	1
104	1.76	2	2	85	1
113	1.69	2	2	85	1
141	1.69	2	2	85	1
169	1.69	2	2	85	1
226	1.69	2	2	85	1

TRT=1 BLQDAY=59 VFDAY=108 Patient=1592 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.95	0	0	1	1
8	2.99	0	0	1	1
15	3.13	0	0	1	1
29	1.89	0	0	1	1
45	1.77	0	0	1	1
59	1.69	1	0	1	1
71	1.69	2	0	71	1
94	1.69	2	0	94	1
108	1.88	2	1	108	1
122	1.70	2	2	108	1
151	1.69	2	2	108	1
178	1.95	2	2	108	1
227	1.69	2	2	108	1

TRT=1 BLQDAY=71 VFDAY=112 Patient=1225 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.42	0	0	1	1
9	3.23	0	0	1	1
15	3.09	0	0	1	1
29	2.60	0	0	1	1
42	1.69	1	0	1	1
55	2.19	0	0	1	1
71	1.69	1	0	1	1
85	1.69	2	0	85	1
100	1.69	2	0	100	1
112	1.71	2	1	112	1
140	1.70	2	2	112	1
168	1.69	2	2	112	1
231	1.69	2	2	112	1
294	1.69	2	2	112	1

TRT=1 BLQDAY=72 VFDAY=282 Patient=1185 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.46	0	0	1	0

9	2.70	0	0	1	0
15	2.32	0	0	1	0
30	1.88	0	0	1	0
44	1.79	0	0	1	0
58	1.76	0	0	1	0
72	1.69	1	0	1	0
86	1.69	2	0	86	0
100	1.71	2	1	100	0
114	1.69	2	0	114	0
142	1.90	2	1	142	0
170	1.69	2	0	170	0
233	1.69	2	0	233	0
282	1.69	2	0	282	0

TRT=1 BLQDAY=85 VFDAY=276 Patient=1766 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.83	0	0	1	0
9	3.27	0	0	1	0
16	2.63	0	0	1	0
29	2.65	0	0	1	0
44	1.69	1	0	1	0
59	2.89	0	0	1	0
75	1.81	0	0	1	0
85	1.69	1	0	1	0
103	1.69	2	0	103	0
120	1.69	2	0	120	0
138	1.76	2	1	138	0
169	1.69	2	0	169	0
221	1.69	2	0	221	0
276	1.69	2	0	276	0

TRT=1 BLQDAY=92 VFDAY=225 Patient=1886 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.37	0	0	1	0
8	3.62	0	0	1	0
15	3.07	0	0	1	0
29	2.73	0	0	1	0
43	2.27	0	0	1	0
57	2.00	0	0	1	0
71	1.72	0	0	1	0
92	1.69	1	0	1	0
99	1.69	2	0	99	0
119	1.78	2	1	119	0
141	1.69	2	0	141	0
169	2.67	2	1	169	0
225	1.69	2	0	225	0

TRT=1 BLQDAY=120 VFDAY=233 Patient=1296 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.59	0	0	1	0
8	4.10	0	0	1	0
16	3.72	0	0	1	0
36	3.23	0	0	1	0

50	3.04	0	0	1	0
64	2.56	0	0	1	0
78	2.57	0	0	1	0
92	2.55	0	0	1	0
106	1.92	0	0	1	0
120	1.69	1	0	1	0
148	1.69	2	0	148	0
176	2.06	2	1	176	0
233	1.69	2	0	233	0

TRT=1 BLQDAY=170 VFDAY=284 Patient=1434 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.51	0	0	1	0
10	3.70	0	0	1	0
16	3.33	0	0	1	0
31	2.90	0	0	1	0
45	2.58	0	0	1	0
59	1.98	0	0	1	0
73	2.82	0	0	1	0
93	2.09	0	0	1	0
102	2.05	0	0	1	0
115	1.76	0	0	1	0
143	2.84	0	0	1	0
170	1.69	1	0	1	0
227	1.69	2	0	227	0
284	1.69	2	0	284	0

TRT=2 BLQDAY=11 VFDAY=285 Patient=1261 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	3.60	0	0	1	0
5	2.22	0	0	1	0
11	1.69	1	0	1	0
25	1.69	2	0	25	0
40	1.69	2	0	40	0
54	1.69	2	0	54	0
68	1.69	2	0	68	0
82	1.69	2	0	82	0
89	1.69	2	0	89	0
110	1.69	2	0	110	0
138	1.73	2	1	138	0
176	1.69	2	0	176	0
228	1.69	2	0	228	0
285	2.13	2	1	285	0

TRT=2 BLQDAY=30 VFDAY=58 Patient=1435 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.00	0	0	1	1
9	3.27	0	0	1	1
16	2.60	0	0	1	1
30	1.69	1	0	1	1
44	1.69	2	0	44	1
58	1.76	2	1	58	1
72	1.71	2	2	58	1

87	1.93	2	2	58	1
100	1.69	2	2	58	1
121	1.69	2	2	58	1
142	1.69	2	2	58	1
170	1.69	2	2	58	1
226	1.69	2	2	58	1
283	1.69	2	2	58	1

TRT=2 BLQDAY=44 VFDAY=272 Patient=1361 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.05	0	0	1	0
8	2.74	0	0	1	0
16	2.05	0	0	1	0
29	1.97	0	0	1	0
44	1.69	1	0	1	0
57	1.69	2	0	57	0
71	1.72	2	1	71	0
85	1.69	2	0	85	0
99	2.00	2	1	99	0
113	1.69	2	0	113	0
141	1.69	2	0	141	0
167	2.10	2	1	167	0
216	1.69	2	0	216	0
272	1.69	2	0	272	0

TRT=2 BLQDAY=46 VFDAY=221 Patient=1593 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.46	0	0	1	0
8	4.20	0	0	1	0
15	3.53	0	0	1	0
32	3.16	0	0	1	0
46	1.69	1	0	1	0
61	1.69	2	0	61	0
72	1.69	2	0	72	0
85	1.69	2	0	85	0
106	1.69	2	0	106	0
110	1.69	2	0	110	0
136	1.92	2	1	136	0
165	1.69	2	0	165	0
221	1.69	2	0	221	0

TRT=2 BLQDAY=58 VFDAY=283 Patient=1825 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	3.87	0	0	1	0
9	3.48	0	0	1	0
16	2.80	0	0	1	0
30	2.64	0	0	1	0
44	1.92	0	0	1	0
58	1.69	1	0	1	0
72	1.69	2	0	72	0
86	1.69	2	0	86	0
100	1.69	2	0	100	0
114	1.69	2	0	114	0

142	1.75	2	1	142	0
170	1.69	2	0	170	0
227	1.69	2	0	227	0
283	1.69	2	0	283	0

TRT=2 BLQDAY=85 VFDAY=280 Patient=1129 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.56	0	0	1	0
8	3.32	0	0	1	0
17	2.71	0	0	1	0
29	2.04	0	0	1	0
44	1.87	0	0	1	0
57	1.82	0	0	1	0
71	1.89	0	0	1	0
85	1.69	1	0	1	0
99	1.69	2	0	99	0
113	1.69	2	0	113	0
143	1.71	2	1	143	0
169	1.69	2	0	169	0
220	1.69	2	0	220	0
280	1.69	2	0	280	0

TRT=2 BLQDAY=85 VFDAY=351 Patient=1286 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.16	0	0	1	0
10	3.88	0	0	1	0
17	3.37	0	0	1	0
36	3.33	0	0	1	0
43	3.22	0	0	1	0
57	2.46	0	0	1	0
71	2.46	0	0	1	0
85	1.69	1	0	1	0
101	1.69	2	0	101	0
113	1.69	2	0	113	0
141	1.70	2	1	141	0
176	1.69	2	0	176	0
232	2.36	2	1	232	0
289	1.69	2	0	289	0
351	1.69	2	0	351	0

TRT=2 BLQDAY=98 VFDAY=217 Patient=1920 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.30	0	0	1	0
9	4.03	0	0	1	0
15	3.65	0	0	1	0
29	3.10	0	0	1	0
44	2.83	0	0	1	0
57	2.84	0	0	1	0
71	2.37	0	0	1	0
85	2.75	0	0	1	0
98	1.69	1	0	1	0
112	1.69	2	0	112	0
140	1.98	2	1	140	0

164	1.69	2	0	164	0
217	2.00	2	1	217	0
282	2.12	2	2	217	0
344	1.69	2	2	217	0

TRT=2 BLQDAY=99 VFDAY=233 Patient=1295 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.83	0	0	1	0
9	3.93	0	0	1	0
16	3.56	0	0	1	0
27	2.92	0	0	1	0
43	2.32	0	0	1	0
58	1.88	0	0	1	0
71	1.69	1	0	1	0
85	1.81	0	0	1	0
99	1.69	1	0	1	0
120	1.69	2	0	120	0
149	1.81	2	1	149	0
177	1.69	2	0	177	0
233	1.69	2	0	233	0

TRT=2 BLQDAY=99 VFDAY=280 Patient=1600 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.74	0	0	1	0
7	3.55	0	0	1	0
15	3.24	0	0	1	0
29	2.56	0	0	1	0
42	2.14	0	0	1	0
57	2.82	0	0	1	0
71	1.83	0	0	1	0
84	1.90	0	0	1	0
99	1.69	1	0	1	0
113	1.69	2	0	113	0
141	1.78	2	1	141	0
169	1.69	2	0	169	0
224	1.69	2	0	224	0
280	1.69	2	0	280	0

TRT=2 BLQDAY=113 VFDAY=218 Patient=1110 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.24	0	0	1	0
8	3.39	0	0	1	0
15	2.60	0	0	1	0
22	1.96	0	0	1	0
43	2.13	0	0	1	0
49	2.51	0	0	1	0
71	1.69	1	0	1	0
85	1.70	0	0	1	0
99	1.90	0	0	1	0
113	1.69	1	0	1	0
134	1.69	2	0	134	0
160	1.75	2	1	160	0
218	1.69	2	0	218	0

TRT=2 BLQDAY=113 VFDAY=224 Patient=1175 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.25	0	0	1	0
9	3.29	0	0	1	0
16	2.89	0	0	1	0
30	3.06	0	0	1	0
44	2.65	0	0	1	0
53	2.00	0	0	1	0
72	2.69	0	0	1	0
85	1.72	0	0	1	0
99	2.09	0	0	1	0
113	1.69	1	0	1	0
141	1.69	2	0	141	0
169	1.89	2	1	169	0
224	1.69	2	0	224	0

TRT=2 BLQDAY=113 VFDAY=281 Patient=1064 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.77	0	0	1	0
8	4.14	0	0	1	0
15	3.26	0	0	1	0
29	2.77	0	0	1	0
43	3.33	0	0	1	0
57	2.58	0	0	1	0
71	1.72	0	0	1	0
85	1.69	1	0	1	0
99	2.22	0	0	1	0
113	1.69	1	0	1	0
141	1.69	2	0	141	0
169	2.07	2	1	169	0
281	1.69	2	0	281	0

TRT=2 BLQDAY=142 VFDAY=235 Patient=1131 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.02	0	0	1	0
10	3.13	0	0	1	0
15	2.69	0	0	1	0
31	1.86	0	0	1	0
46	1.69	1	0	1	0
60	2.19	0	0	1	0
80	2.78	0	0	1	0
94	2.78	0	0	1	0
107	2.34	0	0	1	0
120	2.04	0	0	1	0
142	1.69	1	0	1	0
172	1.69	2	0	172	0
235	2.16	2	1	235	0
284	2.18	2	2	235	0

TRT=2 BLQDAY=168 VFDAY=225 Patient=1003 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.90	0	0	1	0
8	4.33	0	0	1	0

15	4.47	0	0	1	0
30	3.93	0	0	1	0
43	3.34	0	0	1	0
57	3.06	0	0	1	0
71	3.12	0	0	1	0
85	2.62	0	0	1	0
99	2.31	0	0	1	0
113	2.13	0	0	1	0
141	1.85	0	0	1	0
168	1.69	1	0	1	0
225	1.69	2	0	225	0

TRT=2 BLQDAY=168 VFDAY=276 Patient=1168 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.21	0	0	1	0
10	3.91	0	0	1	0
17	3.59	0	0	1	0
31	3.51	0	0	1	0
45	2.42	0	0	1	0
59	2.86	0	0	1	0
70	2.83	0	0	1	0
87	3.87	0	0	1	0
101	2.49	0	0	1	0
115	1.82	0	0	1	0
143	2.15	0	0	1	0
168	1.69	1	0	1	0
224	1.69	2	0	224	0
276	1.69	2	0	276	0

TRT=2 BLQDAY=169 VFDAY=223 Patient=1007 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.59	0	0	1	0
7	4.93	0	0	1	0
15	3.49	0	0	1	0
29	3.51	0	0	1	0
43	3.57	0	0	1	0
55	3.21	0	0	1	0
69	3.01	0	0	1	0
85	2.89	0	0	1	0
97	2.13	0	0	1	0
111	2.01	0	0	1	0
141	1.81	0	0	1	0
169	1.69	1	0	1	0
223	1.69	2	0	223	0

TRT=2 BLQDAY=169 VFDAY=281 Patient=1045 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.78	0	0	1	0
8	4.47	0	0	1	0
15	3.37	0	0	1	0
29	2.92	0	0	1	0
43	3.19	0	0	1	0
57	2.99	0	0	1	0

71	2.59	0	0	1	0
85	2.72	0	0	1	0
99	2.19	0	0	1	0
113	2.74	0	0	1	0
141	1.79	0	0	1	0
169	1.69	1	0	1	0
225	1.69	2	0	225	0
281	1.69	2	0	281	0

TRT=2 BLQDAY=169 VFDAY=281 Patient=1260 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.71	0	0	1	0
8	3.73	0	0	1	0
15	3.29	0	0	1	0
28	2.49	0	0	1	0
43	1.69	1	0	1	0
49	2.29	0	0	1	0
70	2.18	0	0	1	0
82	1.72	0	0	1	0
98	1.94	0	0	1	0
113	1.89	0	0	1	0
138	2.03	0	0	1	0
169	1.69	1	0	1	0
225	1.69	2	0	225	0
281	1.69	2	0	281	0

TRT=2 BLQDAY=169 VFDAY=281 Patient=1644 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.04	0	0	1	0
8	4.39	0	0	1	0
15	3.16	0	0	1	0
29	3.53	0	0	1	0
43	3.11	0	0	1	0
57	2.82	0	0	1	0
71	2.11	0	0	1	0
85	2.72	0	0	1	0
99	2.51	0	0	1	0
113	3.16	0	0	1	0
141	3.32	0	0	1	0
169	1.69	1	0	1	0
225	1.69	2	0	225	0
281	1.69	2	0	281	0

TRT=2 BLQDAY=169 VFDAY=282 Patient=1228 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.47	0	0	1	0
8	3.90	0	0	1	0
16	2.98	0	0	1	0
29	2.77	0	0	1	0
43	1.95	0	0	1	0
58	2.33	0	0	1	0
71	2.90	0	0	1	0
85	1.92	0	0	1	0

99	2.30	0	0	1	0
113	1.69	1	0	1	0
147	2.12	0	0	1	0
169	1.69	1	0	1	0
220	1.69	2	0	220	0
282	1.79	2	1	282	0

TRT=2 BLQDAY=169 VFDAY=346 Patient=1142 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.49	0	0	1	0
8	3.92	0	0	1	0
15	3.29	0	0	1	0
29	3.41	0	0	1	0
43	3.40	0	0	1	0
57	2.90	0	0	1	0
85	1.72	0	0	1	0
95	1.79	0	0	1	0
114	1.69	1	0	1	0
141	2.05	0	0	1	0
169	1.69	1	0	1	0
225	1.69	2	0	225	0
288	1.69	2	0	288	0
346	4.89	2	1	346	0

TRT=2 BLQDAY=169 VFDAY=393 Patient=1424 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	5.02	0	0	1	0
8	2.85	0	0	1	0
15	2.72	0	0	1	0
29	2.13	0	0	1	0
47	2.96	0	0	1	0
57	2.30	0	0	1	0
74	2.00	0	0	1	0
85	2.03	0	0	1	0
99	2.28	0	0	1	0
113	1.95	0	0	1	0
141	2.00	0	0	1	0
169	1.69	1	0	1	0
229	1.69	2	0	229	0
287	1.69	2	0	287	0
337	1.69	2	0	337	0
393	1.69	2	0	393	0

TRT=2 BLQDAY=176 VFDAY=405 Patient=1584 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.52	0	0	1	0
6	4.42	0	0	1	0
16	3.55	0	0	1	0
30	2.77	0	0	1	0
44	2.84	0	0	1	0
58	2.20	0	0	1	0
76	2.85	0	0	1	0
90	2.43	0	0	1	0

98	1.93	0	0	1	0
114	2.00	0	0	1	0
140	1.89	0	0	1	0
176	1.69	1	0	1	0
226	1.69	2	0	226	0
281	1.81	2	1	281	0
338	1.69	2	0	338	0
405	1.69	2	0	405	0

TRT=2 BLQDAY=177 VFDAY=277 Patient=1266 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.68	0	0	1	0
8	4.01	0	0	1	0
15	3.47	0	0	1	0
29	3.00	0	0	1	0
45	2.99	0	0	1	0
60	2.45	0	0	1	0
71	3.00	0	0	1	0
86	1.86	0	0	1	0
100	2.03	0	0	1	0
141	1.83	0	0	1	0
177	1.69	1	0	1	0
228	1.69	2	0	228	0
277	1.69	2	0	277	0

TRT=2 BLQDAY=177 VFDAY=352 Patient=1843 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.98	0	0	1	0
9	3.45	0	0	1	0
16	3.15	0	0	1	0
30	3.79	0	0	1	0
58	2.84	0	0	1	0
72	3.02	0	0	1	0
86	2.16	0	0	1	0
121	1.69	1	0	1	0
149	1.71	0	0	1	0
177	1.69	1	0	1	0
233	1.69	2	0	233	0
296	1.69	2	0	296	0
352	1.69	2	0	352	0

TRT=2 BLQDAY=179 VFDAY=340 Patient=1084 TRT2SD=.

DAY	LOGHIV	BLQ	REBOUND	TFDAY	VFAIL
1	4.23	0	0	1	0
43	2.82	0	0	1	0
60	2.98	0	0	1	0
82	2.71	0	0	1	0
87	2.65	0	0	1	0
101	2.03	0	0	1	0
115	2.08	0	0	1	0
142	1.95	0	0	1	0
179	1.69	1	0	1	0
226	1.69	2	0	226	0

303	1.69	2	0	303	0
340	1.69	2	0	340	0

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Virginia L. Yoerg
Regulatory Health Project Manager
Division of Antiviral Drug Products

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/s/

Virginia Yoerg
12/20/02 09:53:43 AM
CSO

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Steven Gitterman
12/23/02 11:05:45 AM
MEDICAL OFFICER

APPEARS THIS WA
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: December 19, 2002

To: Robin Conrad, Program Director
Drug Regulatory Affairs
Hoffman-La Roche, Inc.

From: Virginia L. Yoerg, Regulatory Health Project Manager, HFD-530

Through: Robert Kumi, Ph.D., Pharmacokinetics Reviewer, HFD-530
Kellie Reynolds, Pharm.D., Pharmacokinetics Team Leader, HFD-530
Melisse Baylor, M.D., Medical Officer, HFD-530
Steven Gitterman, M.D., Medical Team Leader, HFD-530

NDA: 21-481

Drug: Fuzeon (enfuvirtide) for Injection

Subject: Pharmacokinetics comments regarding proposed label

The following comments are being conveyed to you on behalf of Robert Kumi, Ph.D.:

Please provide your justification for making the following comments in the proposed Fuzeon label:

1. Special Populations Section: Gender and Weight (lines 64 and 65)
   "However these changes are not clinically significant and no dose adjustment is required"

2. Drug Interactions Section: Influence of Concomitant Drugs on the Metabolism of Enfuvirtide (Table 1, footnote on line 107)
   **Changes are statistically but not clinically significant.

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Virginia L. Yoerg
Regulatory Health Project Manager
Division of Antiviral Drug Products

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Virginia Yoerg
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Steven Gitterman
12/23/02 11:03:19 AM
MEDICAL OFFICER

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: December 23, 2002

To: Robin Conrad, Program Director
Drug Regulatory Affairs
Hoffman-La Roche, Inc.

From: Virginia L. Yoerg, Regulatory Health Project Manager, HFD-530

Through: Melisse Baylor, M.D., Medical Officer, HFD-530
Steven Gitterman, M.D., Medical Team Leader, HFD-530

NDA: 21-481

Drug: Fuzeon (enfuvirtide) for Injection

Subject: Clinical comments regarding preliminary analyses of infection rates

---

The following comments are being conveyed to you on behalf of Melisse Baylor, M.D as a follow-up to our teleconference held on December 18, 2002.

We examined the results of studies T20-301 and T20-302 for evidence of an increased rate of bacterial infections; this includes both local, site-specific reactions (e.g., cellulitis and abscess) and potential secondary infections (e.g., sepsis). There is also the expectation that as a clinically effective agent, overall exposure-adjusted infections not specific to injection sites would decrease relative to optimized background as a product of drug efficacy. As a new drug class, an immunosuppressive effect could be unrecognizable in studies prior to Phase 3.

To approach this question, we used the Adverse Events datasets provided on CD ROM for T20-301 and T20-302, and defined a cutoff timepoint of 196 days to limit the analysis to the first 24 weeks plus 28 days. We first calculated the overall number of infectious adverse events and number of subjects with infectious adverse events for each treatment group (T-20/optimized background, optimized background, and switch) by identifying every row in the adverse event super class term (AESCT) column that contained the word "infection." We attempted to narrow 'infections' to those that were or could be of presumed bacterial etiology by deleting all infections with the AESCT term of viral, parasitic, or fungal infection. We then eliminated all upper respiratory tract infections, urinary tract infections, sexually transmitted diseases, and infections of unknown etiology that often are due to a viral infection (one example is bronchitis). The adverse event preferred terms (AEPTs) that we classified as bacterial infections were slightly different in T20-301 and T20-302 since slightly different diagnostic terms were used by investigators in these studies. All AEPTs identified in both

studies as bacterial infections are listed below. We are particularly concerned by the increased incidence of pneumonia, sepsis, cellulitis, and abscess in the T-20 group.

T20-301	T20-302
pneumonia	**pneumonia**
abscess	**abscess**
cellulitis	**cellulitis**
sepsis/septic shock	**sepsis/bacteremia**
localized infection	**localized infection**
empyema	**LRT infection**
implant infection	**implant infection**
osteomyelitis	**osteomyelitis**
septic arthritis	**respiratory tract infection**
skin infection	**bronchopneumonia**
Staph infection	**lung infection**
wound infection	**wound infection**
impetigo	**furuncle**
bacterial infection	**bacterial infection**
pyelonephritis	**pyelonephritis**
	tracheitis

As indicated during our December 18, 2002 telephone conversation, our preliminary analysis indicates an increased relative risk for infection in subjects in the T-20 group; it also appears that there is greater infectious risk for subjects after they switch to T-20 (i.e., subjects originally randomized to optimized background therapy). Increased risk for bacterial infection in the T-20 and switch arms was demonstrated first in T20-301, then replicated independently in study T20-302. Based on both the *a priori* approach to this analysis and the replication in T-302 (following analysis of T-301), we consider the outcome from these analyses more strongly than would be suggested by a random, unsystematic analysis of the T-20 safety database.

Again, these are our preliminary analyses, but we felt it was critical to share our concerns with you as soon as possible so that we can work cooperatively to address this issue. We look forward to additional communications regarding this unanticipated finding, including the submission of your independent analyses for our review.

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Virginia L. Yoerg
Regulatory Health Project Manager
Division of Antiviral Drug Products

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Virginia Yoerg
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Steven Gitterman
12/29/02 10:24:25 AM
MEDICAL OFFICER

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: January 2, 2003

To: Cynthia Dillon, Program Director
Drug Regulatory Affairs, CMC
Hoffman-La Roche, Inc.

From: Virginia L. Yoerg, Regulatory Health Project Manager, HFD-530

Through: Stephen P. Miller, Ph.D., Chemistry Team Leader, HFD-530
Rao Kambhampati, Ph.D., Chemistry Reviewer, HFD-530

NDA: 21-481

Drug: Fuzeon (enfuvirtide) for Injection

Subject: Chemistry comments regarding drug substance and drug product

---

The following comments and recommendations are being conveyed on behalf of Rao Kambhampati, Ph.D., regarding the drug substance and drug product for Fuzeon (enfuvirtide) for injection.

If you have any questions about these comments, we encourage you to request a teleconference during the week of January 6, 2003. We are currently discussing the expiration dating period and could possibly provide feedback to you during the aforementioned teleconference.

NDA 21-481 (Fuzeon)

Please address the following chemistry, manufacturing, and controls (CMC) comments and recommendations that are related to the NDA #21-481 for Fuzeon™ (enfuvirtide) for Injection:

Drug Substance:

1) In the Chemical Structure Elucidation section (Vol. 157, pp 53), under [redacted] the Found Mass value and Found Isotope ratio values do not match with those shown in the mass spectrum on page 58. Please provide a detailed interpretation of the mass spectrum.

2) The assay values that were reported in the Batch Analysis Table 2 (Vol. 158, pp 12) for batches BO0103P002, BO0103P008, and BO0104P002 do not match with the values that were reported in the stability data tables for the initial time point. Please provide an explanation for this discrepancy.

3) Out of the [redacted] commercial validation batches, the batches BO0208B007 and BO0208B021 contained [redacted] % and [redacted] % of the [redacted] impurity, respectively, and none detected (nd) level of the [redacted] impurity but the batch BO0208B053 contained nd level of the [redacted] impurity and [redacted] % of [redacted] impurity. Please clarify this anomaly.

4) Please provide amino acid analysis results of batches BO0112P002 and BO0112P003.

5) Please provide results of the stability study that support stability of the drug substance when storage temperature fluctuated between 8°C and ≤25°C for ≥10 days.

6) In the drug substance stability data tables, for batches BO0103P002, BO0103P008, and BO0104P002, the [redacted] impurity was included in the following two isomers, Isomer ([redacted]) and Isomer ([redacted]). Please clarify this discrepancy.

7) For the drug substance stability batch BO0103P002, the [redacted] impurity content decreased to [redacted] at the 12 month time point (4°C) and to [redacted] at the 6 month time point (25°C/60%RH) in comparison to the initial level of [redacted] Please provide an explanation for this phenomenon.

8) For the drug substance stability batch BO0103P008, the Isomer ([redacted]) impurity content decreased to not detected (nd) level at the 12 month (4°C) and 6 month (25°C/60%RH) time points in comparison to the initial level of [redacted] Please provide an explanation for this phenomenon.

9) For the drug substance stability batch BO0103P002, at 4°C storage condition, the following discrepancies were observed: a) the purity decreased from initial level of [redacted] at the 6 month time point and then increased to [redacted], at the 12 month time point; b) the total impurities content increased from an initial level of [redacted] at the 6 month time point and then decreased to [redacted] at the 12 month time point; and c) the assay value decreased from an initial level of [redacted] at the 6 month time point and then increased to [redacted] at the 9 month time point and [redacted] at the 12 month time point. Please provide an explanation.

10) For the drug substance stability batch BO0103P008, at 4°C storage condition, the following discrepancies were observed: a) the purity value decreased from initial level of —— to —— at the 6 month time point and then increased to —— at the 12 month time point; b) the total impurities content increased from an initial level of —— at the 6 month time point and then decreased to —— at the 12 month time point; and c) the assay value decreased from an initial level of —— at the 3 month time point and —— at the 6 month time point and then increased to —— at the 9 month time point and —— at the 12 month time point. Please provide an explanation.

11) In the stability registration batches there was an increase in the co-eluting impurities '—— —— and '—— —— from an initial not detected (nd) level to —— at the 12 month time point (4°C) and to —— at the 6 month time point (25°C/60%RH), therefore, we recommend a higher acceptance criterion of —% for these impurities. The proposed level in the NDA is—— (see Table 1 below).

12) On the basis of the release data provided for—— registration and —— recent Phase 3 clinical batches that represent the commercial manufacturing process, the release data for —— commercial validation batches, and the stability data for —— pilot scale batches that were produced by the commercial manufacturing process, we recommend the following changes to the proposed acceptance criteria for the tests indicated in the Table 1 below (changes are in bold font) for the enfuvirtide drug substance specification.

Table 1:

	Test	*Proposed AC*	*Recommended AC*
	Water[1,2]	Max. 10.0%	**Max. 9.0%**
	Residual solvents: Total	[ ]	[ ]
	Amino acid analysis:		
Amino Acid	Theoretical Eq.		
	Specific rotation		

WITHHOLD 1 PAGE (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: February 13, 2003

To: Cynthia Dillon, Program Director
Drug Regulatory Affairs, CMC
Hoffman-La Roche, Inc.

From: Virginia L. Yoerg, Regulatory Health Project Manager, HFD-530

Through: Stephen P. Miller, Ph.D., Chemistry Team Leader, HFD-530
Rao Kambhampati, Ph.D., Chemistry Reviewer, HFD-530

NDA: 21-481

Drug: Fuzeon (enfuvirtide) for Injection

Subject: Chemistry comments regarding drug substance and drug product

---

The following chemistry, manufacturing, and controls (CMC) comments and recommendations are being conveyed on behalf of Rao Kambhampati, Ph.D., regarding your January 22, 2003 amendment to the NDA 21-481 for Fuzeon (enfuvirtide) for Injection.

Drug Substance:

1. We agree with your submitted responses to our comments and recommendations #1, 3 through 14, and 16.

2. In response to our comment #2, you provided explanation for the purity results instead of the assay results. The differences between the results reported in the batch analysis section and for initial time point in the stability section of the NDA are summarized in the table below. Please provide an explanation for the discrepancies.

Drug Substance Batch No.	Reported Assay Result at Release in Batch Analysis Table (Vol. 158, pp 162)	Reported Assay Result for Initial Time Point (T=0) in Stability Data Tables (Vol. 158, pp. 241, 243, and 245)
BO0103P002	[redacted] area %	[redacted] area %
BO0103P008	[redacted] area %	[redacted] area %
BO0104P002	[redacted] area %	[redacted] area %

Drug Product:

3. With regard to our comment #15, for Total of All Degradation Products we propose a revised acceptance criterion in the range of maximum —— area %, which is based on the following observations:

   a) The maximum amount of Total of All Degradation Products (including unspecified) actually observed in the registration batches (Basel and ———— sites) and in the Roche, Basel commercial scale validation batches = —— area %

   b) The maximum increase of Total of All Degradation Products (including unspecified) actually observed after 6 months of storage at 40°C/75%RH (per your interpretation, it is equivalent to 24 months of storage at 25°C/60%RH) = —— area %.

   The newly proposed range of maximum —— area % is ———— higher than the actual values observed for the registration and commercial scale batches.

In addition, we agree with your proposed expiration dating period of 24 months for Fuzeon vials that are stored at 25°C (77°C).

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Virginia L. Yoerg
Regulatory Health Project Manager
Division of Antiviral Drug Products

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/s/

Virginia Yoerg
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CSO

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Stephen Paul Miller
2/19/03 10:37:15 AM
CHEMIST

From: Yoerg, Virginia L
Sent: Thursday, January 23, 2003 3:36 PM
To: Robin Conrad {PDR~Nutley} (E-mail)
Cc: Yoerg, Virginia L
Subject: January 22, 2003 tcon: DAVDP information request

Robin,

We received your response about the increased risk of pneumonia and sepsis in subjects receiving T-20 in studies T20-301 and T20-302 and have determined that additional information is needed for our application review. During the teleconference today, we committed to provide the content of our information request to you via e-mail. Please provide the following as soon as possible:

- additional data including the mortality rates, incidence of AIDS defining events, and incidence of bacterial infections, particularly pneumonia and sepsis, in studies 301 and 302 (that occurred after the data cutoff for the safety update report). This should include the 'snapshot' of available data as discussed on 1/22 from which these analyses would be generated; we would appreciate the data being submitted as soon as possible, even if this precedes the analyses cited above.
- a more detailed analysis of the risk factors for infection including baseline CD4 count, change in CD4 count, change in viral load, virologic failure, and absolute neutrophil count.
- association of the risk of infection with gender, smoking, age, or alcohol use.
- analysis of concomitant medication use including antibiotic use overall, use of individual antibiotics and classes of antibiotics, use of antibiotics for prophylaxis, reason for prophylaxis, and use of other concomitant medications.
- a more detailed analysis of the risk of infection in switch subjects, including correction for exposure and the analyses described previously.
- narratives for all patients with bacterial infections from studies 301 and 302.

We would also much appreciate discussion and/or submission of any additional analyses you consider relevant to this particular issue that have not been raised in earlier discussions. We look forward to your response.

Virginia L. Yoerg
Regulatory Health Project Manager
FDA/DAVDP

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/s/

Virginia Yoerg
3/2/03 10:46:34 AM
CSO

information request sent via email on 1/23/03, clinical request regarding apparent increased risk of pneumonia and sepsis.

Steven Gitterman
3/4/03 08:15:11 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Katrin Rupalla, Ph.D.
Senior Program Manager
Drug Regulatory Affairs
Hoffmann-La Roche, Inc.
340 Kingsland Street
Nutley, NJ 07110-1199

RE: NDA 21-481
Fuzeon™ (enfuvirtide) for Injection
MACMIS ID # ——

Dear Dr. Rupalla:

This letter responds to a request submitted by Hoffmann-La Roche Inc. to the Division of Drug Marketing, Advertising, and Communications (DDMAC) for proposed launch promotional material advisory on January 8, 2003. The following items were reviewed:

1. Revised Injection Instruction Sheet
    - paper, disk, and final layout copy

2. Patient Starter Kit/Travel Pak
    - Fuzeon planner
    - Preparation mat
    - "Your guide to taking Fuzeon" flip chart
    - Introduction letter
    - "How to Prepare and Inject FUZEON" video outer carton
    - Travel sharps container
    - Injection practice pad
    - Travel cards (pocket and normal size)

3. "How to Prepare and Inject Fuzeon" video script and storyboard

4. Health Care Provider Kit box
    - Introduction letter
    - Fuzeon patient education checklist
    - "Fuzeon - A Health Care Provider's Patient Education Guide" flip chart
    - "Patient Education Materials" envelope

- "Your Guide to Taking Fuzeon" flip chart
- Fuzeon planner
- Caregiver's guide to injecting Fuzeon
- Injection instruction sheet
- "How to Prepare and Inject Fuzeon" video outer carton
- Injection practice supplies outer carton

DDMAC offers the following comments, which apply to this as well as future materials containing similar claims or presentations.

[

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[

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[

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[

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[

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[

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Total of all	Max. ——	area%)	**Max. ——**	**(area%)**

[1]Test also performed on stability testing
AC=Acceptance criterion

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Virginia L. Yoerg
Regulatory Health Project Manager
Division of Antiviral Drug Products

Drug Product:

13) Enfuvirtide drug substance degrades at the rate of [redacted] per year (NDA Vol. 158, pp 223) when stored at 25°C/60%RH but the drug product degrades at the rate of only [redacted] per year when stored under the same conditions. Please provide an explanation for the increased stability of the drug product.

14) In the specification for the drug product, the proposed acceptance criterion for the Ro 29-9800 (enfuvirtide) content per vial is [redacted] which corresponds to an average value of 105.3 mg (97.5%). Since each Fuzeon vial is expected to contain an average of 108 mg of enfuvirtide, we propose an acceptance criterion of [redacted] of Ro 29-9800 per vial (see Table 2 below).

15) The proposed Total Degradation Products content in the drug product specification is [redacted] The released registration batches contained in the range of 2.84-3.31% and after 12 months storage at 25°C/60%RH the levels increased in the range of 0.38-0.66% and after 6 months storage at 40°C/75%RH the levels increased in the range of 0.56-0.75%. On the basis of these observations, we propose an acceptance criterion of [redacted] for the Total Degradation Products content in the drug product specification (see Table 2 below).

16) On the basis of the release data provided for [redacted] registration batches [redacted] pilot size and [redacted] commercial size) and the stability data for [redacted] registration batches, we recommend the following changes to the proposed acceptance criteria for the tests indicated in the Table 2 (changes are in bold font) below for the Fuzeon drug product specification:

Table 2

Test	*Proposed AC*	*Recommended AC*
Content per vial of Ro 29-9800	[redacted] mg [redacted]	[redacted] **mg** [redacted]
Degradation Products Identified with (±0.01):		
[redacted]	Max [redacted] (area%)	**Max. [redacted] (area%)**
[redacted]	Max [redacted] (area%)	**Max. [redacted] (area%)**
[redacted]	Max [redacted] (area%)	**Max. [redacted] (area%)**
[redacted]	Max [redacted] area%)	**Max. [redacted] (area%)**
[redacted]	Max. [redacted] (area%)	**Max. [redacted] (area%)**
[redacted]	Max. [redacted] (area%)	**Max. [redacted] (area%)**
[redacted]	Max. [redacted] (area%)	**Max. [redacted] (area%)**
[redacted]	Max. [redacted] (area%)	**Max. [redacted] (area%)**
[redacted]	Max. [redacted] (area%)	**Max. [redacted] (area%)**
[redacted]	Max. [redacted] (area%)	**Max. [redacted] (area%)**
Others, each	Max. [redacted] (area%)	**Max. [redacted] (area%)**
Others, Total	Max. [redacted] (area%)	Max. [redacted] (area%)

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/s/

Virginia Yoerg
1/2/03 02:51:13 PM
CSO

hard copy signed and faxed to applicant

Stephen Paul Miller
1/21/03 10:01:14 AM
CHEMIST

APPEARS THIS WAY
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WITHHOLD 3 PAGE (S)

Katrin Rupalla
Hoffmann-La Roche Inc.
NDA 21-481
MACMIS # ——

[ ]

[ ]

Sincerely,

{See appended electronic signature page}

Debi Tran, Pharm.D.
LT, USPHS
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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/s/

Debi Tran
2/21/03 08:46:14 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: February 27, 2003

To: Robin Conrad, Program Director
Drug Regulatory Affairs
Hoffman-La Roche, Inc.

From: Virginia L. Yoerg, Regulatory Health Project Manager, HFD-530

Through: Stephen P. Miller, Ph.D., Chemistry Team Leader, HFD-530
Rao Kambhampati, Ph.D., Chemistry Reviewer, HFD-530

NDA: 21-481

Drug: Fuzeon (enfuvirtide) for Injection

Subject: Chemistry comments

The following comments and recommendations regarding NDA 21-481 are being conveyed on behalf of Drs. Peter Cooney and James McVey, of CDER's Product Quality Microbiology Staff.

Microbiology Deficiencies and Comments

In your response, you may reference an approved application using the same sterilization equipment and cycle.

A) Regarding the ——— manufacturing at Hoffman-La Roche:

1. Please provide the sterile filtration validation data. Include the pre and post filtration integrity test results and the limits included in the production outline or batch production record. Provide the actual microbial challenge data demonstrating the effect of the challenge on the filter and the effect of the product on the challenge organism.

2. Regarding the validation of the equipment and packaging component sterilization, the following information should be provided for each cycle validated:

   •

- [
-
-
-
-
]

3. Regarding the validation of the compounding and receiving tank sterilization, the following information should be provided for each cycle validated:

- [
-
-
-
-

4

5.

6.

7.]

B) Regarding the —— manufacturing at ——

1. [redacted]

2. [redacted]

3. Regarding the validation of the equipment and packaging component sterilization, the following information should be provided for each cycle validated:

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

4. [redacted]

5. [redacted]

6. [redacted]

7. [redacted]

8. [redacted]

C) [redacted] – No concerns were raise with respect to DMF [redacted] for the manufacture of the [redacted]

Please inform Virginia Yoerg, Regulatory Health Project Manager, at (301) 827-2335 about your expected response time. If a teleconference would be useful to discuss these issues, we will arrange for one at the earliest opportunity.

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Virginia L. Yoerg
Regulatory Health Project Manager
Division of Antiviral Drug Products

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/s/

Virginia Yoerg
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fax sent to applicant

Stephen Paul Miller
2/28/03 04:33:52 PM
CHEMIST

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: March 7, 2003

To: Robin Conrad, Program Director
Drug Regulatory Affairs
Hoffman-La Roche, Inc.

From: Virginia L. Yoerg, Regulatory Health Project Manager, HFD-530

Through: Jeff O'Neill, ACRN, Regulatory Project Manager, HFD-530
Steven Gitterman, M.D., Ph.D., Medical Team Leader, HFD-530

NDA: 21-481

Drug: Fuzeon (enfuvirtide) for Injection

Subject: Suggested revisions to the Fuzeon patient education materials

---

The Division of Antiviral Drug Products recommends the following revisions to the Fuzeon patient education materials, including the Patient Starter Kit/Travel Pak and the Health Care Provider Kit. See attached review.

General:

1. Please refer to the approved PPI for appropriate content for all patient education materials. Information in your educational materials must be consistent with the approved PPI.

2. Some of your materials refer to the healthcare provider and some to the doctor or physician. Wording should be changed to healthcare provider. Please make certain that this wording is changed on all your educational materials.

We are providing this information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Virginia L. Yoerg
Regulatory Health Project Manager
Division of Antiviral Drug Products

Educational Materials
NDA 21-481, Fuzeon™ (enfuvirtide)

Date completed: March 7, 2003

Materials Reviewed: ***Patient Starter Kit/Travel Pak*** *(Your Guide to Taking FUZEON Flip Chart, Preparation Mat, Welcome Letter, Travel Cards, Fuzeon Planner, Caregiver's Guide to Injecting FUZEON, Injection Instructions, Injection practice pad, Travel sharps container, How to Prepare and Inject FUZEON Video)*

Health Care Provider Kit *(Welcome Letter, FUZEON – A Health Care Provider's Patient Education Guide, FUZEON Patient Education Checklist, Your Guide to Taking FUZEON, FUZEON Planner, Caregiver's Guide to Injecting FUZEON, Injection Instruction Sheet)*

Sponsor: Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, N.J. 07110

Drug: Fuzeon (enfuvirtide)

Formulation: Lypholized Powder 90 mg for injection

Indication: Treatment of HIV

General comments:

1. Please refer to the approved PPI for appropriate content for all patient education materials. Information in your educational materials must be consistent with the approved PPI.

2. Some of your materials refer to the healthcare provider and some to the doctor or physician. Wording should be changed to healthcare provider. Please make certain that this wording is changed on all your educational materials.

Patient Education Guide "Your Guide to Taking Fuzeon™"

The following changes are suggested for Your Guide to Taking FUZEON™ and should be consistent with all patient educational materials.

Page one:

At our Sept. 4th meeting you agreed to add the sentence "This guide reinforces what you learned at your healthcare provider's office".

All the tabs in this document, while intended to encourage patients should be removed or taken only from approved wording in the Patient Package Insert (please refer to communications from our Division of Drug Marketing, Advertising and Communications (DDMAC). In general, we favor the tabs and titles themselves since these help organize the information.

Page three:

We suggest adding the following sentence in order to direct patients to the more comprehensive instructions:

- See the **FUZEON** ***Injection Instructions*** section for step-by-step instructions about how to inject FUZEON.

We suggest the following bulleted sentence be added to this page:

- When your FUZEON supply runs low, be sure to have it refilled. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. If you miss or skip doses of FUZEON, HIV may develop resistance to FUZEON and become harder to treat.

Eliminate the second sentence, third bulleted item, currently on page 3 (beginning with "). This second sentence is replaced by the suggestion above. Retain the first sentence in this bulleted item.

Page five:

You have listed the less severe side effects first; we advise listing the more serious side effects first.

In the first paragraph, you instruct patients to, ——————————————————————. This sentence may urge patients to feel they need to report even minor symptoms to their healthcare provider immediately. A better way to word this may be, "Report any new or continuing symptoms to your health care provider."

Please make the following information more prominent:

> **(Bold)FUZEON can cause serious allergic reactions**. Symptoms of a serious allergic reaction with FUZEON can include:
>
> **(add bullets to)**
> - Trouble breathing
> - Fever with vomiting and a skin rash
> - Blood in your urine
> - Swelling of your feet
>
> **(put in bold)Call your healthcare provider right away if you get any of these symptoms.**

Page eight:

[ ]

[ ]

[ ]

Please include reference numbers on pages eight and nine. These pages do not indicate the study that the percentages are derived from. On page 23 under ***Safety Information*** the following references are listed: ***1.*** *TORO 1 Study Group, Enfuviritide (T-20) in combination with an optimized background (OB) regimen vs. OB alone in patients with prior experience or resistance to each of the three classes of approved ARVs in North America and Brazil (TORO 1), and* ***2.*** *TORO 2 Study Group, Enfuvirtide (T-20) in combination with and optomized background (OB) regimen vs. OB alone in patients with prior experience or resistance to each of the three classes of approved ARVs in Europe and Australia* (TORO 2).... We assume that this is the source of the information on pages eight and nine. If so, this should be referenced.

Page ten:

Under the heading, ——— We recommend the following changes:

[ ]

Page seventeen:

In the third sentence, under the section ——— the sentence reads ———

——— Consider changing the sentence to read ———

This will help avoid confusion as to which vial you are referring to in the sentence.

The following information is specific to the piece of educational material reviewed:

[ ]

FUZEON Patient Education Checklist

Please add signs and symptoms of an allergic reaction to your checklist.

How to Prepare and Inject FUZEON Video

Please consider including some information about Injection Site Reactions. The video is a good opportunity to show pictures, explain about injection sites and instruct patients about emergent reactions. It would also be helpful to include information about how to handle side effects (tylenol for pain, benadryl for itching, etc.).

You may also want to consider showing the web site as a super imposed image and directing patients to seek further information at the site.

Additional Comments

You may wish to consider supplying patient FUZEON kits with extra needles above the minimum needed since wastage is likely.

[ ]

Patients will require a sharps container that is large enough to hold the amount of needles they will use between visits (We assume that most clients will return sharps containers to their providers office).

Please create a more specific instruction guide for caregivers of pediatric patients. Although the existing guide indirectly addresses issues in pediatric patients, a more specific targeted booklet is likely to be more effective in communicating information to these pediatric caregivers.

_____
Jeff D. O'Neill, RN, ACRN
Regulatory Project Manager
Division of Antiviral Drug Products

Concurrence
HFD-530/MOTL/Gitterman

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/s/

Jeff ONeill
3/7/03 04:52:56 PM
CSO
Review of educational material for FUZEON (enfuvirtide)
Review of educational material for FUZEON (enfuvirtide)

Steven Gitterman
3/7/03 05:21:48 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: March 7, 2003

To: Robin Conrad, Program Director
Drug Regulatory Affairs
Hoffman-La Roche, Inc.

From: Virginia L. Yoerg, Regulatory Health Project Manager, HFD-530

Through: Nara Battula, Ph.D., Microbiology Reviewer, HFD-530
Jules O'Rear, Ph.D., Microbiology Team Leader, HFD-530
Rao Kambhampati, Ph.D., Chemistry Reviewer, HFD-530
Stephen P. Miller, Ph.D., Chemistry Team Leader, HFD-530
William Taylor, Ph.D., Pharmacology/Toxicology Reviewer, HFD-530
James Farrelly, Ph.D., Pharmacology/Toxicology Team Leader, HFD-530
Robert Kumi, Ph.D., Pharmacokinetics Reviewer, HFD-530
Kellie Reynolds, Pharm.D., Pharmacokinetics Team Leader, HFD-530
Thomas Hammerstrom, Ph.D., Statistics Reviewer, HFD-530
Greg Soon, Ph.D., Statistics Team Leader, HFD-530
Melisse Baylor, M.D., Medical Officer, HFD-530
Steven Gitterman, M.D., Ph.D., Medical Team Leader, HFD-530

NDA: 21-481

Drug: Fuzeon (enfuvirtide) for Injection

Subject: Fuzeon postmarketing commitments

The Division of Antiviral Drug Products requests that you fulfill the following postmarketing commitments for NDA 21-481. When appropriate, please add the time estimates (Ideal Format) for each commitment. At minimum, propose a completion date for each commitment and submit your proposal by Monday, March 10, 2003.

Ideal Format:

Description of Commitment:

Protocol Submission:	Within X months of the date of this letter
Study Start:	Within Y months of the date of this letter
Final Report Submission:	Within Z months of the date of this letter

If you have questions regarding these commitments, please contact me.

Clinical and Pharmacology/Toxicology

Due to a possible imunosuppressive effect of enfuvirtide, as manifest by an increase in the incidence of bacterial respiratory infections in enfuvirtide-treated patients (enfuvirtide plus optimized background) versus patients on optimized background in Phase 3 clinical trials, we have the following clinical and pharmacology/toxicology requests:

1. Please submit for review the complete protocol for the clinical cohort study you have described in outline form, "Proposed postmarketing observational cohort study." FDA expects that following review by FDA, this study will be initiated shortly after the product launch of enfuvirtide and completed in a time frame specified in the protocol.

2. Please conduct nonclinical immune function studies to investigate whether enfuvirtide causes immunosuppression. Such studies could help to elucidate the mechanism of immunosuppression, provide information for risk evaluation, and possibly indicate biomarkers for monitoring clinical status. Please conduct a general-purpose immune suppression screening assay such as a T-cell dependent antibody-forming assay, and a more specific host resistance assay using an appropriate animal model for upper-respiratory bacterial infections. A final report from these studies should be submitted within twelve months of the date of this letter.

Additional Clinical Requests

3. [redacted]

4. [redacted]

Pharmacokinetics

5. Provide additional pharmacokinetic data in children less than six years old.

6. Evaluate the effect of impaired renal function (creatinine clearance less than 35 mL/minute) on enfuvirtide pharmacokinetics.

7. Determine the mechanism of the drug-drug interaction between ritonavir and enfuvirtide; depending on the outcome, additional drug-drug interaction studies may be necessary.

Microbiology

8. In 20% (42/207) of the patients experiencing virologic failure while on Fuzeon, HIV envelope protein has switched and/or broadened its coreceptor usage. If the changes in coreceptor usage are greater in the T-20 arm than the control arm, please evaluate the effect of the alterations in the viral tropism on potential changes in virulence. Please submit your evaluation within 18 months of the date of this letter.

9. In virologic failures, please sequence the entire gp160 sequence of paired isolates to identify the genetic determinants that contribute to the phenotypic resistance. Please submit your results within 15 months of the date of this letter.

Chemistry, Manufacturing, and Controls

10. Please make efforts to increase the ——— of the ——— drug substance to approximately ——— by making changes to the current synthesis and purification procedures.

11. Per your amendments dated 1/22/03 and 2/27/03, please reevaluate the currently agreed-upon acceptance criteria for ——— in the drug substance specification and for ——— products in the drug product specification after manufacturing additional batches of the ——— substance and drug product during the next year. Please report your conclusions, and any recommended changes to the acceptance criteria, using the submission recommendations in the Guidance on *"Changes to an Approved NDA or ANDA."*

We are providing this information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

[/S/]

Virginia L. Yoerg
Regulatory Health Project Manager
Division of Antiviral Drug Products

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/

Virginia Yoerg
3/12/03 03:54:39 PM
CSO

hardcopy faxed to applicant on 3/7/03

Steven Gitterman
3/12/03 04:01:50 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

March 12, 2003

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Division Document Room N115
9201 Corporate Boulevard
Rockville, MD 20850

Dear Dr. Birnkrant:

Re: NDA 21-481 - Fuzeon™ (enfuvirtide, Ro 29-9800) for Injection
Response to Proposed Post Marketing Commitments

Reference is made to Hoffmann-La Roche Inc.'s New Drug Application NDA 21-481 for Fuzeon (enfuvirtide, Ro 29-9800) for Injection. Reference is also made to a teleconference with the Agency on March 12, 2003 regarding postmarketing commitments for Fuzeon.

As agreed with the Agency during the teleconference, the Sponsor is not being asked at this time to commit to postmarketing drug-drug interaction studies. We understand, however, that based on postmarketing experience with Fuzeon the Sponsor may be asked to address other drug-drug interactions at a later date.

Should you have any questions concerning this submission, please feel free to contact the undersigned.

Sincerely,

HOFFMANN-LA ROCHE INC.

Robin L. Conrad
Group Director
Drug Regulatory Affairs
(973) 562-3676 (phone)
(973) 562-3700 (fax)

APPEARS THIS WAY
ON ORIGINAL

RLC/dpg
HLR No. 2003-790

Desk Copy: Virginia Yoerg

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF INTERNAL MEETING

Date of Meeting: **October 2, 2002**

NDA: **NDA 21-481**

Drug: **Fuzeon™ (enfuvirtide) injection**

Applicant: **Hoffman-La Roche, Inc.**

Indication: **Treatment of HIV-1 infection**

Participants:
Debra B. Birnkrant, M.D., DAVDP Director
Jeffrey Murray, M.D., DAVDP Deputy Director
Melisse Baylor, M.D., Medical Officer
Kassa Ayalew, M.D., Medical Officer
Stephen Miller, Ph.D., Chemistry Team Leader
Rao Kambhampati, Ph.D., Chemistry Reviewer
Greg Soon, Ph.D., Statistics Team Leader
Tom Hammerstrom, Ph.D., Statistics Reviewer
Kellie S. Reynolds, Pharm.D., Biopharmaceutics Team Leader
Robert Kumi, Ph.D., Biopharmaceutics Reviewer
James Farrelly, Ph.D., Pharmacology/Toxicology Team Leader
Jules O'Rear, Ph.D., Microbiology Team Leader
Narayana Battula, Ph.D., Microbiology Reviewer
Virginia L. Yoerg, Regulatory Health Project Manager
Jeff O'Neill, Regulatory Project Manager

Type of Meeting: Filing Meeting

Related Documents: IND ——— and NDA 21-481

Background: Hoffman-La Roche, Inc. initiated rolling review (Subpart H-Accelerated Approval, under 21 CFR 314.500) with their June 24, 2002 submission, and triggered the PDUFA clock with their final component of the rolling NDA dated September 13, 2002, received September 16, 2002. The additional submissions to the rolling NDA were dated June 26, 2002, July 1, 2002, July 16, 2002, July 24, 2002, July 30, 2002, August 13, 2002, August 22, 2002, and September 10, 2002. The applicant has paid the user fee in full. The internal action goal date for this NDA is early February, 2003 and the six month PDUFA date is March 16, 2003.

This NDA is for Fuzeon™ (enfuvirtide) administered subcutaneously for the treatment of HIV-1 infection, in combination with other antiretroviral agents. Fuzeon was licensed from Trimeris Inc. by Hoffman-La Roche, Inc., and is the first drug in a new pharmacologic class (fusion inhibitors). This meeting was held to determine whether the application is filable.

Discussion

1. Pharmacology/Toxicology

Dr. Farrelly stated that the NDA is filable.

2. Microbiology

Dr. Battula stated that the NDA is filable.

3. Chemistry

Dr. Kambhampati stated that the NDA is filable.

4. Biopharmaceutics/Clinical Pharmacokinetics

Dr. Kumi stated that the NDA is filable. A pharmacometrics consult was sent.

5. Clinical

Dr. Baylor stated that there are no filing issues, and therefore the application is filable.

6. Statistics

Dr. Hammerstrom stated that the application is filable.

7. Standard or Priority Review

The applicant requested a priority review. DAVDP will grant this application a priority review.

8. Advisory Committee Meeting

DAVDP determined that although enfuvirtide is the first drug in a new pharmacologic class (fusion inhibitors), an advisory committee meeting is **not** necessary.

9. Division of Scientific Investigations (DSI)

A consult was sent to DSI on August 3, 2002, requesting that Inspection Summary Results be provided by December 5, 2002. DAVDP requested inspection of clinical sites essential for NDA approval.

10. Patient Education

The patient package insert, package insert, and injection instruction sheets should be finalized by the action letter date. However, under Subpart H, the additional patient education materials (considered launch materials) must be cleared by the Division of Drug Marketing and Communications prior to launch, but not necessarily before an action letter can be issued. Additionally, the review team will consider replacing the patient package insert with a Medication Guide.

11. Pediatric Rule

The Pediatric Rule is automatically triggered with this NDA. The applicant requested deferral of pediatric studies for age groups birth to six months until June, 2006 and a deferral for infants from six to 36 months until June, 2004. In the NDA, the applicant stated that a deferral for ages through 16 was not requested because data on patients in this age group was included in the NDA, and studies are ongoing in this patient group.

Conclusions

- The review team concluded that NDA 21-481 is filable, and is designated as a priority review (six month clock).

Action Items

- A consult will be sent to the Office of Drug Safety (ODS) for tradename review. The tradename, Fuzeon, was cleared by the Office of Post-Marketing and Drug Risk Assessment (OPDRA) in a consult review dated September 28, 2001, but an additional review must be conducted 90 days prior to NDA approval.

- The review team will revisit the possibility of issuing a Medication Guide instead of a patient package insert.

- DAVDP will inform the applicant that a priority review was granted.

Minutes Preparer: Virginia L Yoerg, October 2, 2002

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/s/

Steven Gitterman
10/9/02 03:47:11 PM

APPEARS THIS WAY
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

RECORD OF INTERNAL MEETING

MEETING DATE: January 15, 2003
TIME: 11a.m. LOCATION: Corporate S400
REVIEW DIVISION: HFD-530, Division of Antiviral Drug Products (DAVDP)

NDA:	**21-481**
Drug:	**Fuzeon™ (enfuvirtide) for injection**
Proposed Indication:	**Treatment of HIV-1 infection**
Applicant:	**Hoffman-LaRoche, Inc.**

Type of Meeting: Pre-approval Safety Conference

ODE 4 Participants:

Mark J. Goldberger, M.D., Director
David Roeder, M.S., Associate Director for Regulatory Affairs

DAVDP Participants:

Jeffrey Murray, M.D., Deputy Director
Steven Gitterman, M.D., Ph.D., Medical Team Leader
Melisse Baylor, M.D., Medical Reviewer
Virginia L. Yoerg, Regulatory Project Manager
Andrea James, M.D., Medical Officer
Anthony DeCicco, R.Ph., Chief, Project Management Staff

ODS Participants:

Allen Brinker, M.D., Medical Officer/Epidemiology
Paula Gish, Safety Evaluator
Debbie Boxwell, Safety Evaluator
Quynh Nguyen, Regulatory Project Manager

Meeting Objective: To provide an update to the Office of Drug Safety regarding the Fuzeon™ (enfuvirtide) safety issues prior to NDA approval.

Background: Fuzeon (enfuvirtide), previously know as T-20, is the first antiretroviral agent to inhibit fusion of HIV to CD4+ cells. Ninety milligrams of enfuvirtide is administered twice daily by subcutaneous injection. Two Phase 3 studies were submitted in this NDA as support for the safety and efficacy of Fuzeon. Clinical trial T20-301 was conducted at 48 centers in US, Canada, Brazil, and Mexico (December, 2000 through December, 2001) and trial T20-302 was conducted

at 67 centers in Western Europe and Australia (February, 2001 through January, 2002). This NDA was granted rolling review, and the PDUFA goal date is March 16, 2003.

Discussion:

Dr. Baylor summarized the efficacy results and presented the following safety issues:

1. Adverse Events (AEs)/ Serious Adverse Events (SAEs)

Diarrhea, nausea, and fatigue were the most common AEs in T20-301 (all were more common in the optimized background (OB) group) and the most common AEs in T20-302 were diarrhea and nausea (also more common in OB group). In T20-301, peripheral neuropathy and decreased appetite occurred with ≥5% greater incidence in T-20/OB arm than in OB arm.

Increased CPK, increased GGT, neutropenia, anemia, pancreatitis, and pyrexia were the only SAEs that occurred in more than 2% of subjects receiving T-20 in T20-301.

2. Injection Site Reaction (ISR)

Injection site reactions were the most common AEs associated with the use of enfuvirtide. They were experienced by 98% of subjects in Phase 3 studies. They usually occurred in the first week (>80%) and continued to occur throughout the use of enfuvirtide (>60% at each study visit had an ISR).

The most common signs and symptoms of ISRs were pain (≥95%) erythema (≥89%), induration (≥89%), and nodules/cysts (≥76%). Less commonly seen signs and symptoms included pruritis (≥63%) and bruising (≥50%). However, complications from ISRs were minimal. Some study subjects and health care providers attempted to alleviate the signs and symptoms of ISRs using various treatments (6% in T20-301), but it is unclear how to best treat ISRs.

3. Hypersensitivity Reaction

Hypersensitivity reactions have included rash, fever, nausea, vomiting, chills, rigors, low blood pressure, and elevated liver function tests (LFTs). A small number of hypersensitivity reactions recurred on rechallenge. The applicant has alerted their investigators about possible hypersensitivity reactions via Dear Health Care Professional letters. Also, information about hypersensitivity reactions will be included in the package insert for enfuvirtide.

4. Pancreatitis

An increase in the incidence of pancreatitis was noted in T20-301 but not T20-302, and increased incidence of Grade 3 and Grade 4 amylase and lipase laboratory values were seen in both Phase 3 studies.

5. Psychiatric Signs and Symptoms

Six study subjects in T20-302 discontinued the study because of depression. Other subjects

experienced stress and anxiety while taking Fuzeon. In some subjects the stress and anxiety was attributed to difficulties with self injection and/or ISRs.

6. Bacterial Infections

We examined the results of studies T20-301 and T20-302 for evidence of an increased rate of bacterial infections; this includes both local, site-specific reactions (e.g., cellulitis and abscess) and potential secondary infections (e.g., sepsis) but not ISRs. Preliminary analysis indicated an increased incidence of bacterial infections in subjects in the enfuvirtide group; it also appeared that there was an increased incidence of bacterial infections in subjects on OB treatment who switched to enfuvirtide. Increased risk for bacterial infection in the enfuvirtide and switch arms was demonstrated first in T20-301, then replicated independently in study T20-302. Based on both the *a priori* approach to this analysis and the replication in T20-302 (following analysis of T20-301), the outcome from these analyses is considered more strongly than would be suggested by a random, unsystematic analysis of the T-20 safety database.

Actions:

- DAVDP will request more information from the applicant regarding the apparent increased incidence of bacterial infections in patients exposed to enfuvirtide.
- DAVDP will consult with other medical officers in the ODE about this increased incidence of bacterial infections.

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/s/

Jeffrey Murray
3/4/03 04:49:38 PM

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