CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-322

Administrative/Correspondence Reviews

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation or Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-322

NAME OF APPLICANT / NDA HOLDER
Serono, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME
Luveris

ACTIVE INGREDIENT(S)	STRENGTH(S)
recombinant human luteinizing hormone	75 IU

DOSAGE FORM	APPROVAL DATE OF NDA OR SUPPLEMENT
lyophilized powder	

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) within thirty (30) days after approval of an NDA or supplement or within thirty (30) days of issuance of a patent as required by 21 CFR 314.53(c)(2)(ii) at the address provided in 21 CFR 314.53(d)(4). To expedite review of this patent declaration form, you may submit an additional copy of this declaration form to the Center for Drug Evaluation and Research "Orange Book" staff.

For hand-written or typewriter versions of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the approved NDA or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this NDA or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,767,251	06/16/1998	06/16/2015

d. Name of Patent Owner
Genzyme Corporation

Address *(of Patent Owner)*
500 Kendall Street

City/State
Cambridge, MA

ZIP Code	FAX Number *(if available)*
02139	
Telephone Number	**E-Mail Address *(if available)***
(617) 252-7500	

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Pamela Williamson Joyce
Serono, Inc.

Address *(of agent or representative named in 1.e.)*
One Technology Place

City/State
Rockland, MA

ZIP Code	FAX Number *(if available)*
02370	(781) 681-2947
Telephone Number	**E-Mail Address *(if available)***
(781) 982-9000	

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☑ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☑ No

For the patent referenced above, provide the following information on each patent that claims the drug substance, drug product, or method of use that is the subject of the approved NDA or supplement. FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing. FDA will consider an incomplete patent declaration to be a declaration that does not include a response to all the questions contained within each section below applicable to the patent referenced above.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the approved NDA or supplement?	☑ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA?	☐ Yes	☑ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the approved active ingredient? (Complete the information in section 4 below if the patent claims an approved method of using the approved drug product to administer the metabolite.)	☐ Yes	☑ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☑ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

FDA will not list the patent in the Orange Book as claiming the drug substance if:

- **the answers to 2.1 and 2.2 are "No," or,**
- **the answer to 2.2 is "Yes" and the answer to 2.3 is "No," or,**
- **the answer to 2.3 is "Yes" and there is no response to 2.4, or,**
- **the answer to 2.5 or 2.6 is "Yes."**
- **the answer to 2.7 is "No."**

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the approved drug product as defined in 21 CFR 314.3?	☐ Yes	☑ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☑ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

FDA will not list the patent in the Orange Book as claiming the drug product if:

- **the answer to question 3.1 is "No," or,**
- **the answer to question 3.2 is "Yes," or,**
- **the answer to question 3.3 is "No."**

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming an approved method of using the approved drug product. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more approved methods of using the approved drug product?	☐ Yes	☑ No
4.2 Patent Claim Number *(as listed in the patent)* — Does the patent claim referenced in 4.2 claim an approved method of use of the approved drug product?	☐ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify the use with specific reference to the approved labeling for the drug product. — Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*		

4.2b If the answer to 4.2 is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description.	Use: *(Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.)*

FDA will not list the patent in the Orange Book as claiming the method of use if:

- **the answer to question 4.1 or 4.2 is "No," or**
- **if the answer to 4.2 is "Yes" and the information requested in 4.2a and 4.2b is not provided in full.**

5. No Relevant Patents

For this NDA or supplement, there are no relevant patents that claim the approved drug substance (active ingredient) or the approved drug product (formulation or composition) or approved method(s) of use with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official)* *(Provide information below)*	Date Signed
	10/08/2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☑ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Serono, Inc.	
Address Rockland, MA 02370	City/State Rockland, MA
ZIP Code 02370	Telephone Number (781) 982-9000
FAX Number *(if available)* (781) 681-2947	E-Mail Address *(if available)*

Department of Health and Human Services
Food and Drug Administration

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ACTIVE INGREDIENT(S)	STRENGTH(S)
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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,650,390	07/22/1997	07/22/2014

d. Name of Patent Owner	Address *(of Patent Owner)*	
Applied Research Systems ARS Holding N.V. (a wholly owned subsidiary of Serono)	15, Pietermaai, Curaçao, Netherlands Antilles	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
Pamela Williamson Joyce Serono, Inc.	One Technology Place	
	City/State Rockland, MA	
	ZIP Code 02370	FAX Number *(if available)* (781) 681-2947
	Telephone Number (781) 982-9000	E-Mail Address *(if available)*

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Address Rockland, MA 02370	City/State Rockland, MA
ZIP Code 02370	Telephone Number (781) 982-9000
FAX Number *(if available)* (781) 681-2947	E-Mail Address *(if available)*

13. PATENT INFORMATION

Information for patents on the Drug Substance (ingredient), Drug Product (formulation and composition), and Method of Use is provided below. The following Patent information is provided in accordance with the Drug Price and Patent Term Restoration Act of 1984:

Tradename:	Luveris™
Active Ingredient:	Recombinant human luteinizing hormone
Strength(s):	75 IU
Dosage Form:	Lyophilized powder for injection

Patent Information

U.S. Patent Number:	U.S. Patent No. 5,767,251
Expiration Date:	June 16, 2015
Type of Patent:	Drug Substance (recombinant gonadotropins)
Name of patent owner:	Genzyme Corporation

A copy of US Patent No. 5,767,251 is appended.

US Patent No. 5,767,251 was issued in the name of Genzyme Corporation, the successor to Integrated Genetics, Inc. Pursuant to the Purchase and License Agreement between Integrated Genetics, Inc. and Ares-Serono, Inc. of June 6, 1989, US Patent No. 5,767,251 remains the property of Integrated Genetics, Inc. or its successors, but Ares-Serono, Inc. and its affiliates, including Serono, Inc., have a worldwide exclusive irrevocable royalty-free license to this patent.

U.S. Patent Number:	U.S. Patent No. 5,650,390
Expiration Date:	July 22, 2014
Type of Patent:	Drug Product (formulation)
Name of patent owner:	Applied Research Systems ARS Holding N.V. (a wholly owned subsidiary of Serono)

A copy of US Patent No. 5,650,390 is appended.

US005767251A

United States Patent [19]

Reddy et al.

[11] Patent Number: 5,767,251

[45] Date of Patent: Jun. 16, 1998

[54] **RECOMBINANT HETERODIMERIC HUMAN FERTILITY HORMONES, AND METHODS, CELLS, AND VECTORS AND DNA FOR THE PRODUCTION THEREOF**

[75] Inventors: **Vemuri B. Reddy**, Westboro; **Nancy Hsiung**, Wellesley, both of Mass.; **Anton K. Beck**, Grisbeladierbeg, Switzerland; **Edward George Berustine**, Boston, Mass.

[73] Assignee: **Genzyme Corporation**, Cambridge, Mass.

[21] Appl. No.: 8,233

[22] Filed: Jan. 22, 1993

Related U.S. Application Data

[60] Division of Ser. No. 515,481, Apr. 27, 1990, abandoned, which is a continuation-in-part of Ser. No. 323,772, Mar. 15, 1989, abandoned, and Ser. No. 696,647, Jan. 30, 1985, Pat. No. 4,923,805, which is a continuation of Ser. No. 548,228, Nov. 2, 1993, Pat. No. 4,840,896, said Ser. No. 323,772, is a continuation of Ser. No. 548,228.

[51] Int. Cl.[6] C07K 14/59

[52] U.S. Cl. 530/397; 435/69.4; 424/198.1

[58] Field of Search 435/69.4; 530/397, 530/398, 350, 351, 412–417; 536/23.1, 23.51; 424/198.1

[56] References Cited

U.S. PATENT DOCUMENTS

4,383,034	5/1983	Sugimoto .	
4,419,446	12/1983	Howley et al. .	
4,468,464	8/1984	Cohen et al. .	
4,656,134	4/1987	Ringold	435/91
4,840,896	6/1989	Reddy et al. .	
4,923,805	5/1990	Reddy et al.	435/69.4

FOREIGN PATENT DOCUMENTS

2139631 10/1984 United Kingdom .

OTHER PUBLICATIONS

Rathman et al., *The Journal of Biological Chemistry* 250(17):6735–6746 (1975).

Saxena et al., *The Journal of Biological Chemistry* 251(4):993–1005 (1976).

Pierce et al., *Ann. Rev. Bioch.* 50:465–496 (1981).

Fiddes et al., *Nature* 286:684–687 (1980).

Chappel, S. et al., *Endocrine Reviews* 4(2):179–211 (1983).

Fiddes et al., *J. Mol. Appl. Gene* 1:3–18 (1981).

Elder, J.T. et al., *Ann. Rev. Genet.* 15:328–330 (1981).

Rice, D. et al., *Proc. Natl. Acad. Sci.* 79:7862–7865 (1982).

Moriarty, A. et al., *Proc. Natl. Acad. Sci.* 78:2606–2610 (1981).

Lusthader, J. et al., 68th Annual Meeting of the Endocrine Society, Abstract #513.

Stewart, F. "Application of Recombinant DNA Techniques to Structure–Function Studies of Equine Protein Hormones", *Chemical Abstracts* 108(3):147, col. 1–2, Abstract No. 17058w (1987).

Nilson, J., "Expression of the Genes Enchoding Bovine LH in a Line of Chinese Hamster Ovary Cells", *Chemical Abstracts* 107(17):187, col. 2, Abstract No. 148529C (1987).

Schwartzbouer, J., "Efficient and Stable Expression of Recombinant Fibronectin Polypeptides", *Chemical Abstracts* 106:173, col. 1, Abstract No. 132796f (1987).

Reddy, V., "Heterodimeric Human Fertility Hormones", *Chemical Abstracts* 103(7):146, col. 1, Abstract No. 49165d (1985).

Reddy, V., "Heterodimeric Human Fertility Hormones", *Chemical Abstracts* 103(9):182, col. 1–2, Abstract No. 66081d (1985).

Kaetzel, D. et al., "Methotrexate–Induced Amplification of the Bovine Lutropin Genes in Chinese Hamster Ovary Cells. Relative Concentration of the Alpha and Beta Subunits Determines the Extent of Heterodimer Assembly", *J. Biol. Chem.* 263:6344–6351(1988).

Kaetzel, D. et al., "Expression of Biologically Active Bovine Luteinizing Hormone in Chinese Hamster Ovary Cells", *Proc. Natl. Acad. Sci. USA* 82:7820–7823 (1985)

Kato, Y., "Cloning and DNA Sequence Analysis of the cDNA for the Precurson of Porcine Follicle Stimulating Hormone Beta Subunit", *Chemical Abstracts* 109(7):182, col. 2, Abstract No. 49432a (1988).

Fujiki et al. (1980) Biochimica et Biophysica Acta, 624, pp. 428–435.

Rathnam et al (1971) JBC, vol. 246, No. 23, pp. 7087–7094.

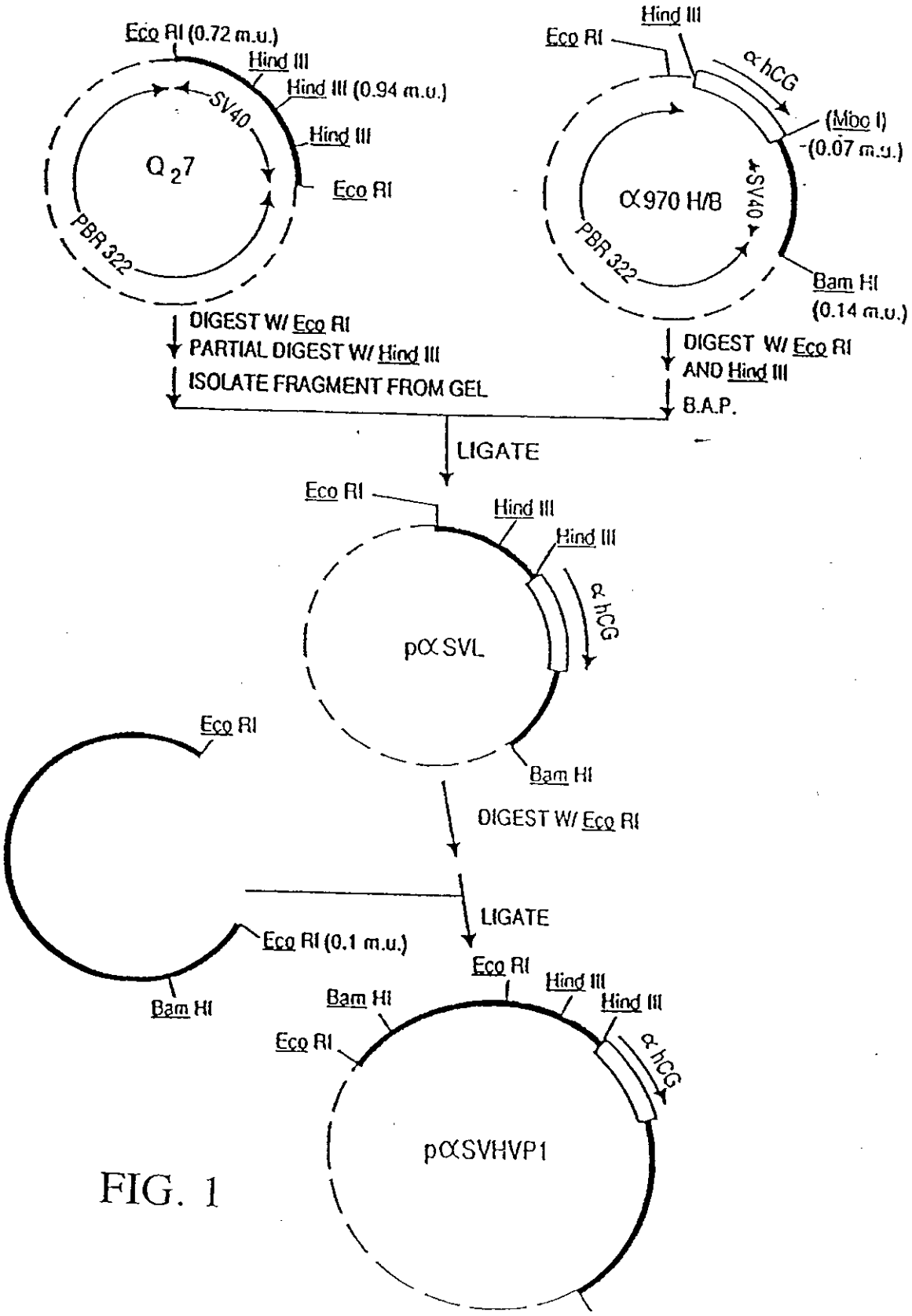
Morgan et al. (1971) Endocrinology, vol. 88, No. 4, pp. 1045–1053.

Primary Examiner—Stephen Walsh
Assistant Examiner—Lorraine M. Spector
Attorney, Agent, or Firm—Browdy and Neimark

[57] **ABSTRACT**

Biologically active heterodimeric human fertility hormones composed of two different subunits, each subunit being synthesized in the same cell transformed by at least one cell expression vector having heterologous DNA encoding each subunit with each subunit being controlled by a separate promoter. Preferred human fertility hormones include hCG, hLH and hFSH.

4 Claims, 13 Drawing Sheets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Eco RI
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α970 H/B
SV40
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(0.14 m.u.)
DIGEST W/ Eco RI
AND Hind III
B.A.P.
LIGATE
Eco RI
Hind III
Hind III
α hCG
pαSVL
Bam HI
Eco RI
DIGEST W/ Eco RI
LIGATE
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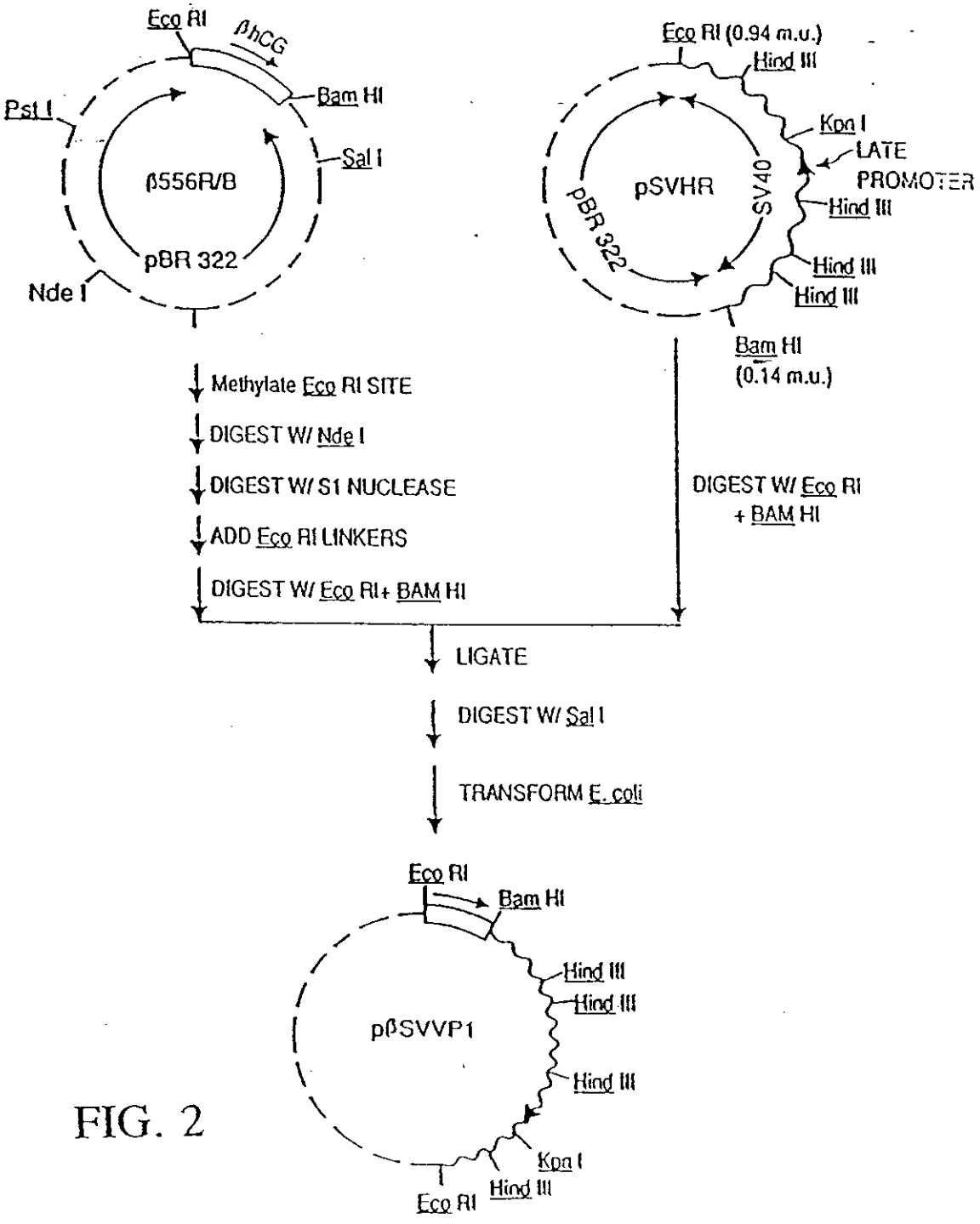
FIG. 1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Methylate Eco RI SITE
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DIGEST W/ S1 NUCLEASE
ADD Eco RI LINKERS
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DIGEST W/ Eco RI + BAM HI
LIGATE
DIGEST W/ Sal I
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Hind III
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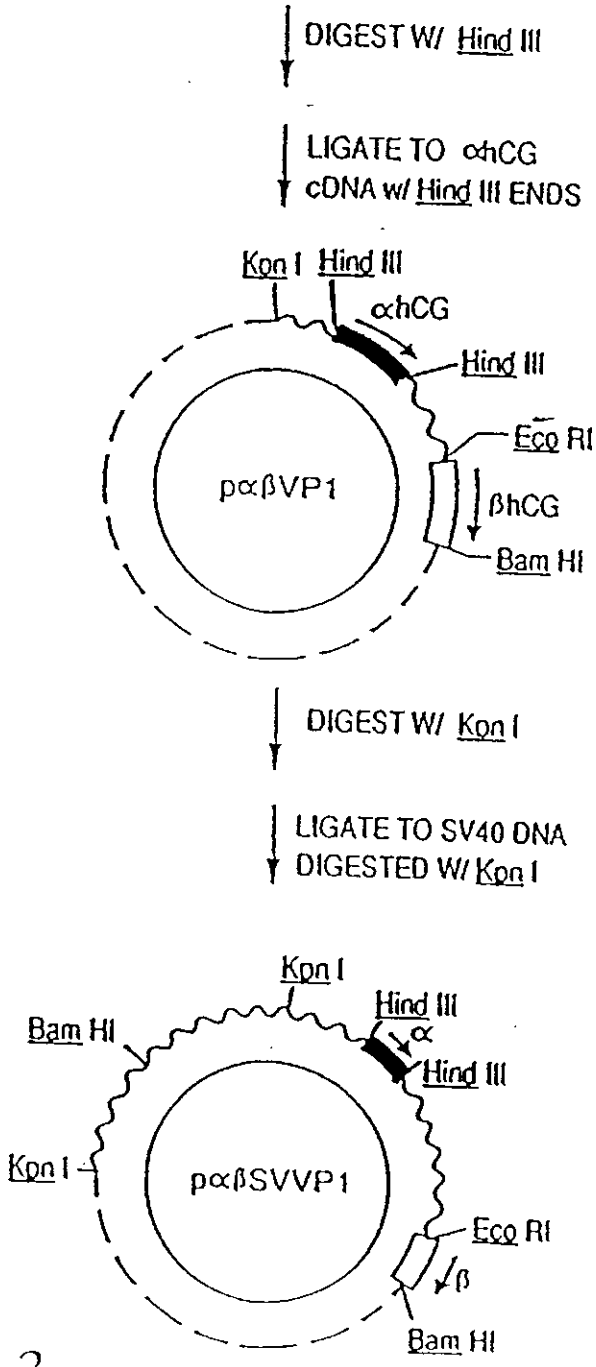
Kpn I
Hind III
Eco RI

FIG. 2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LIGATE TO αhCG
cDNA w/ Hind III ENDS
Kpn I
Hind III
αhCG
Hind III
Eco RI
pαβVP1
βhCG
Bam HI
DIGEST W/ Kpn I
LIGATE TO SV40 DNA
DIGESTED W/ Kpn I
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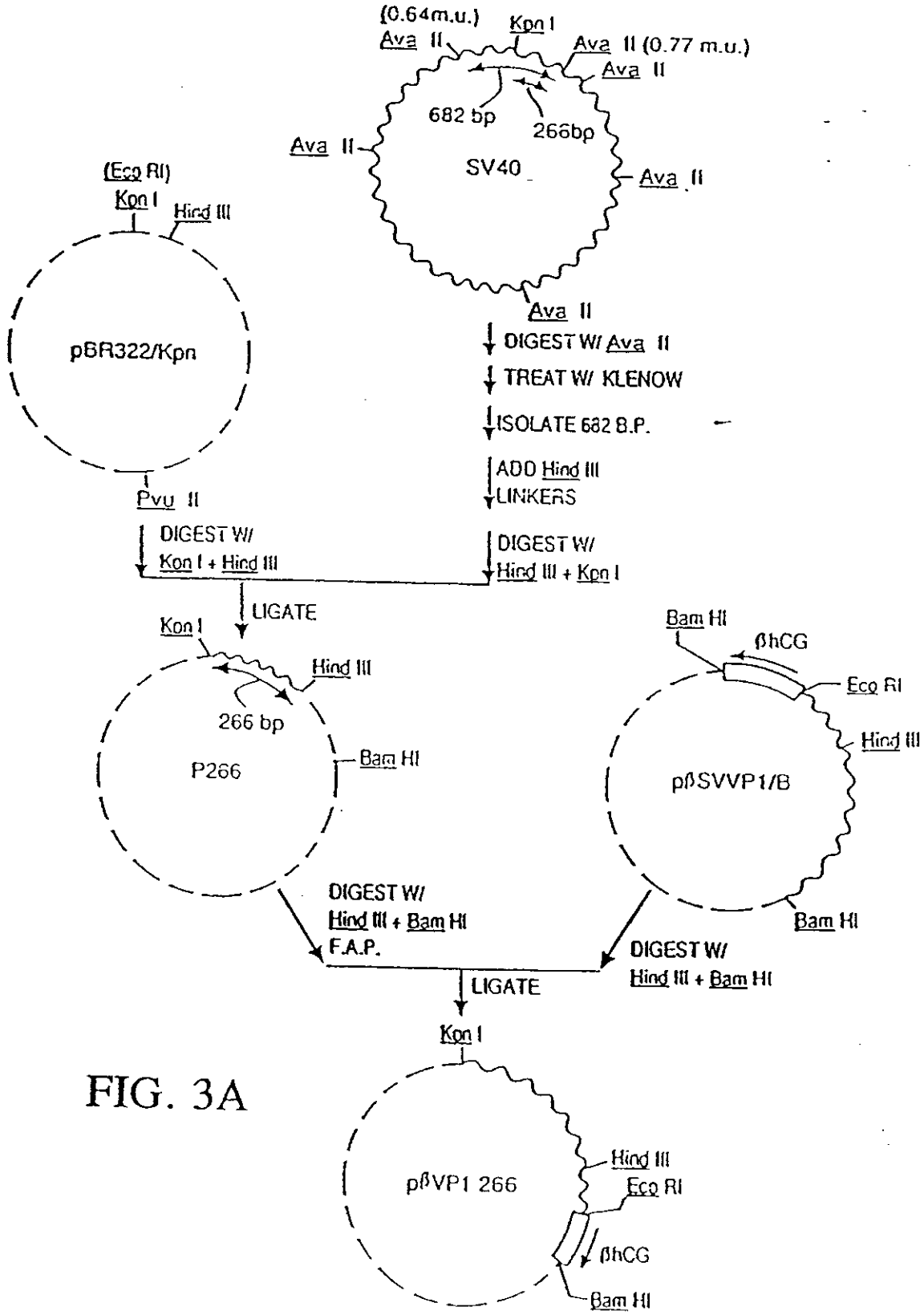
Bam HI

FIG. 3


(0.64m.u.)
Ava II
Kpn I
Ava II (0.77 m.u.)
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682 bp
266bp
Ava II
SV40
Ava II
Ava II
DIGEST W/ Ava II
TREAT W/ KLENOW
ISOLATE 682 B.P.
ADD Hind III LINKERS
(Eco RI)
Kpn I
Hind III
pBR322/Kpn
Pvu II
DIGEST W/ Kpn I + Hind III
DIGEST W/ Hind III + Kpn I
LIGATE
Kpn I
Hind III
266 bp
P266
Bam HI
Bam HI
βhCG
Eco RI
Hind III
pβSVVP1/B
Bam HI
DIGEST W/ Hind III + Bam HI F.A.P.
DIGEST W/ Hind III + Bam HI
LIGATE
Kpn I
pβVP1 266
Hind III
Eco RI
βhCG
Bam HI

FIG. 3A

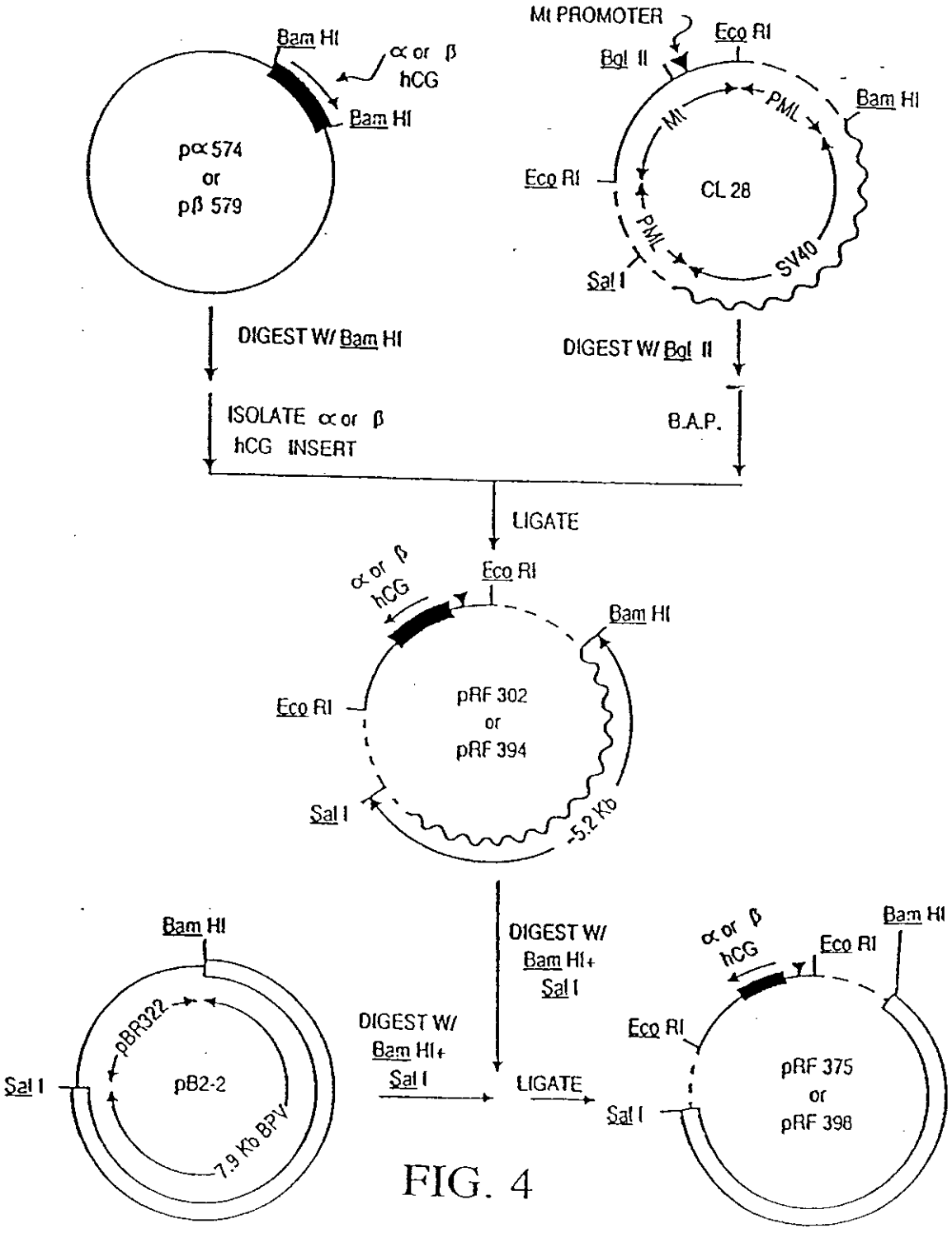

Bam HI
α or β hCG
Bam HI
pα574 or pβ 579
DIGEST W/ Bam HI
ISOLATE α or β hCG INSERT
Mt PROMOTER
Eco RI
Bgl II
Bam HI
Mt
PML
CL 28
Eco RI
PML
SV40
Sal I
DIGEST W/ Bgl II
B.A.P.
LIGATE
α or β hCG
Eco RI
Bam HI
Eco RI
pRF 302 or pRF 394
Sal I
-5.2 Kb
DIGEST W/ Bam HI + Sal I
DIGEST W/ Bam HI + Sal I
LIGATE
Bam HI
pBR322
Sal I
pB2-2
7.9 Kb BPV
α or β hCG
Eco RI
Bam HI
Eco RI
pRF 375 or pRF 398
Sal I

FIG. 4

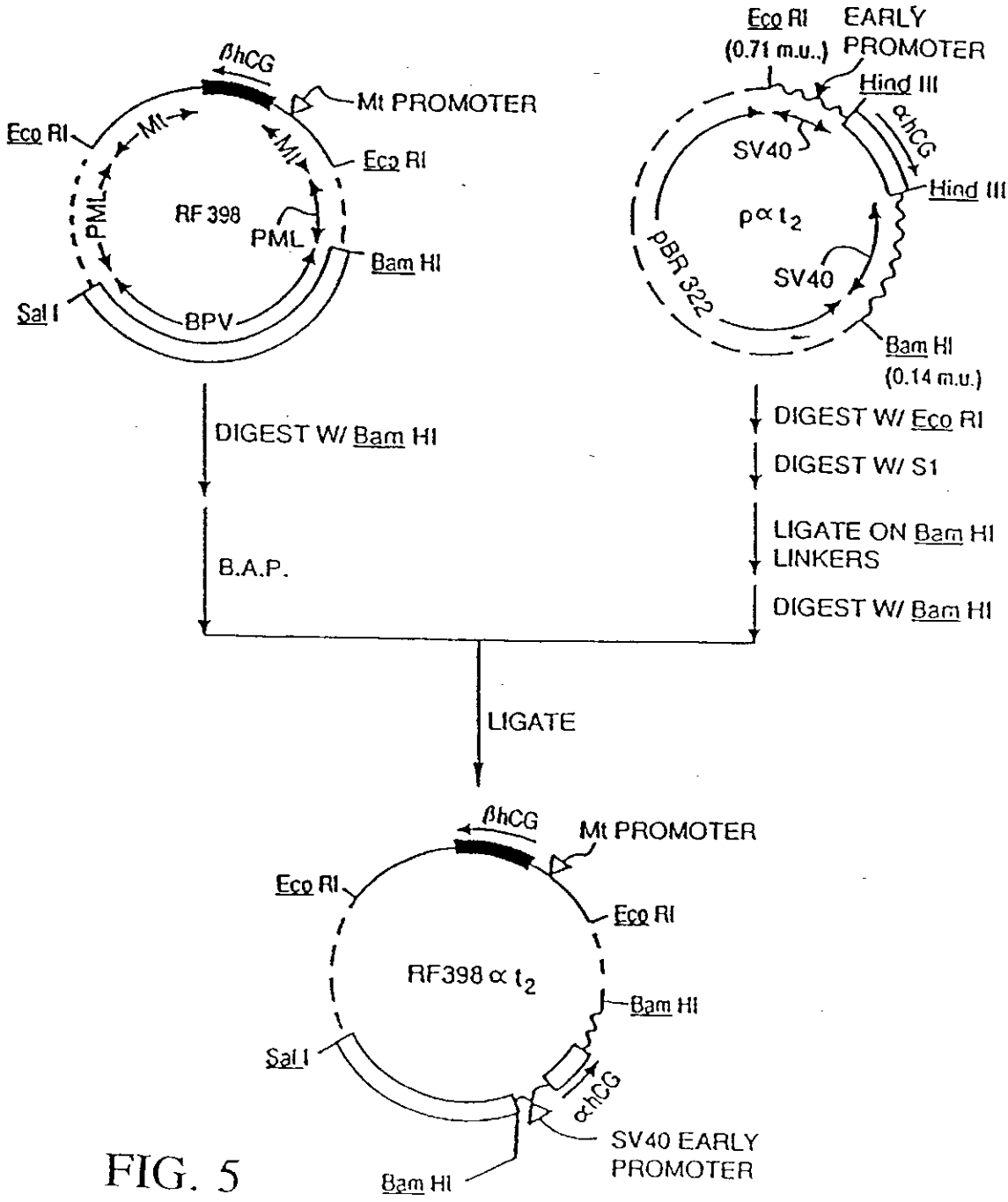

βhCG
Mt PROMOTER
Eco RI
Mt
Mt
Eco RI
PML
RF 398
PML
Bam HI
Sal I
BPV
Eco RI (0.71 m.u.)
EARLY PROMOTER
Hind III
αhCG
Hind III
SV40
pαt2
pBR 322
SV40
Bam HI (0.14 m.u.)
DIGEST W/ Bam HI
B.A.P.
DIGEST W/ Eco RI
DIGEST W/ S1
LIGATE ON Bam HI LINKERS
DIGEST W/ Bam HI
LIGATE
βhCG
Mt PROMOTER
Eco RI
Eco RI
RF398 αt2
Bam HI
Sal I
αhCG
SV40 EARLY PROMOTER
Bam HI

FIG. 5

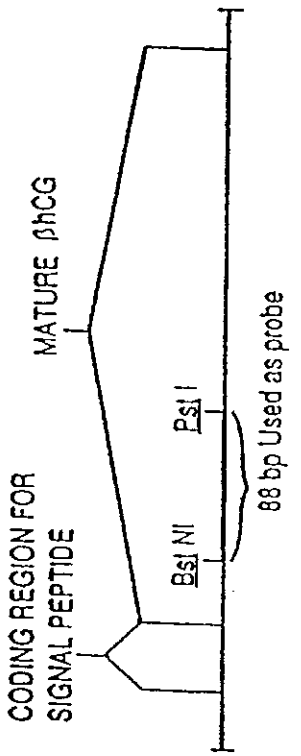

MATURE βhCG
CODING REGION FOR SIGNAL PEPTIDE
Pst I
Bst NI
88 bp Used as probe

FIG. 6

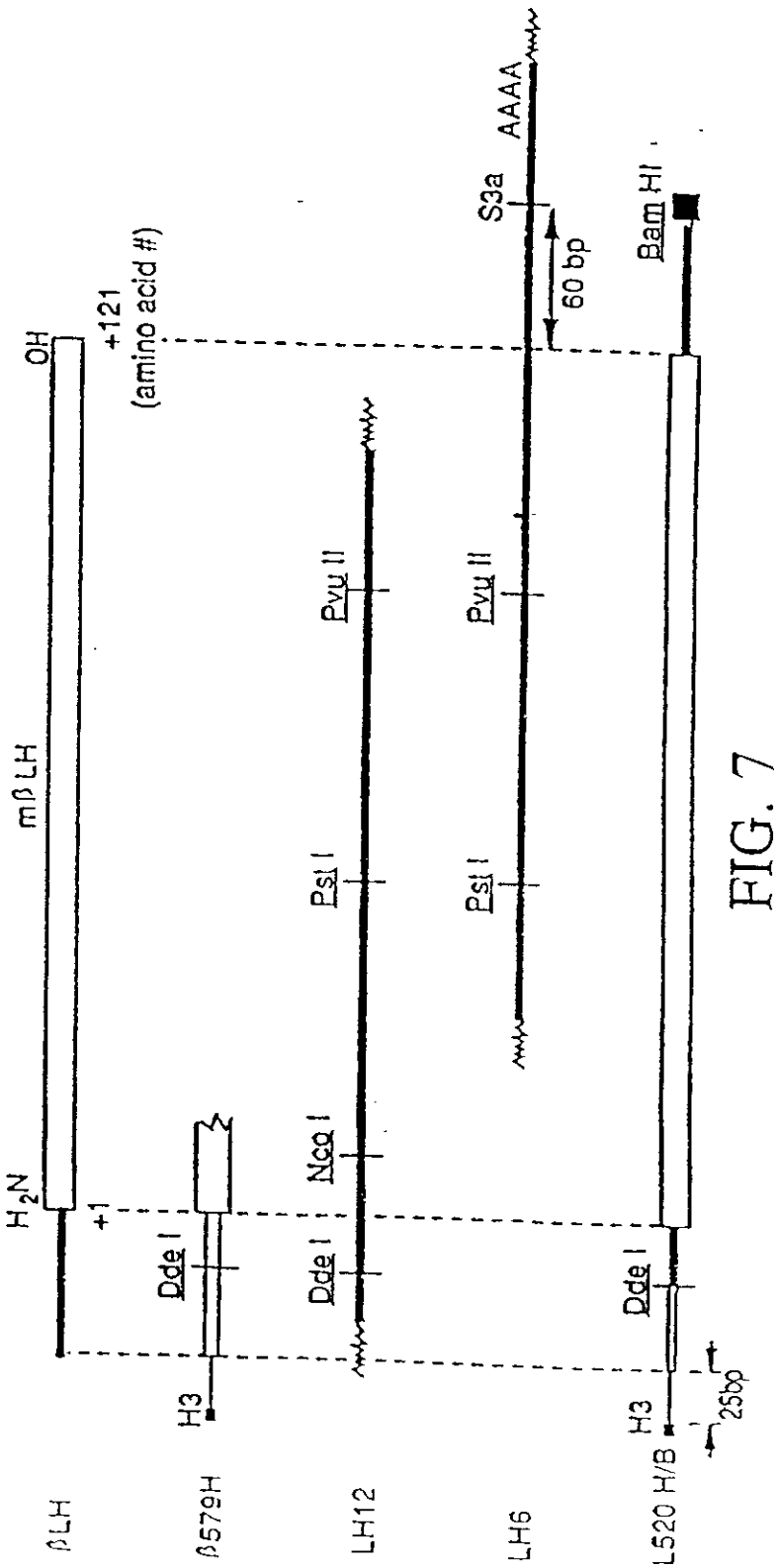

OH
+121 (amino acid #)
mβ LH
H_2N
+1
Pvu II
Pst I
Ncq I
Dde I
H3
S3a
AAAA
60 bp
Bam HI
25bp
βLH
β579H
LH12
LH6
L520 H/B

FIG. 7

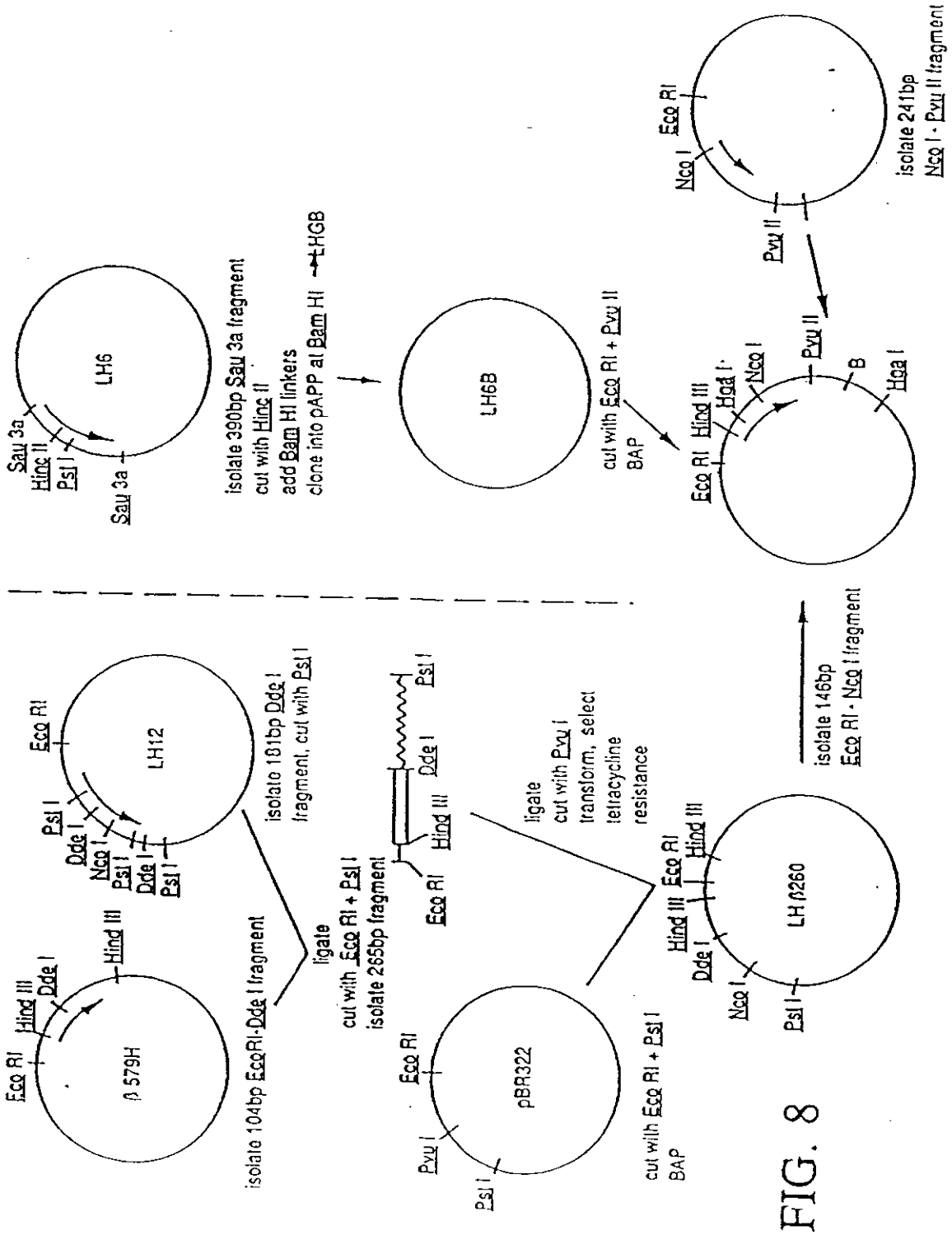

LH6
Sau 3a
Hinc II
Pst I
Sau 3a
isolate 390bp Sau 3a fragment
cut with Hinc II
add Bam HI linkers
clone into pAPP at Bam HI
HGB
LH6B
cut with Eco RI + Pvu II
BAP
Eco RI
Hind III
Hpa I
Nco I
Pvu II
B
Hpa I
Pvu II
Nco I
Eco RI
isolate 241bp
Nco I - Pvu II fragment
LH12
Eco RI
Pst I
Dde I
Nco I
Pst I
Dde I
Pst I
isolate 181bp Dde I
fragment, cut with Pst I
β 579H
Eco RI
Hind III
Dde I
Hind III
isolate 104bp EcoRI-Dde I fragment
ligate
cut with Eco RI + Pst I
isolate 265bp fragment
Eco RI
Hind III
Dde I
Pst I
pBR322
Eco RI
Pvu I
Pst I
ligate
cut with Pvu I
transform, select
tetracycline
resistance
cut with Eco RI + Pst I
BAP
LH 8260
Eco RI
Hind III
Hind III
Dde I
Nco I
Pst I
isolate 146bp
Eco RI - Nco I fragment

FIG. 8

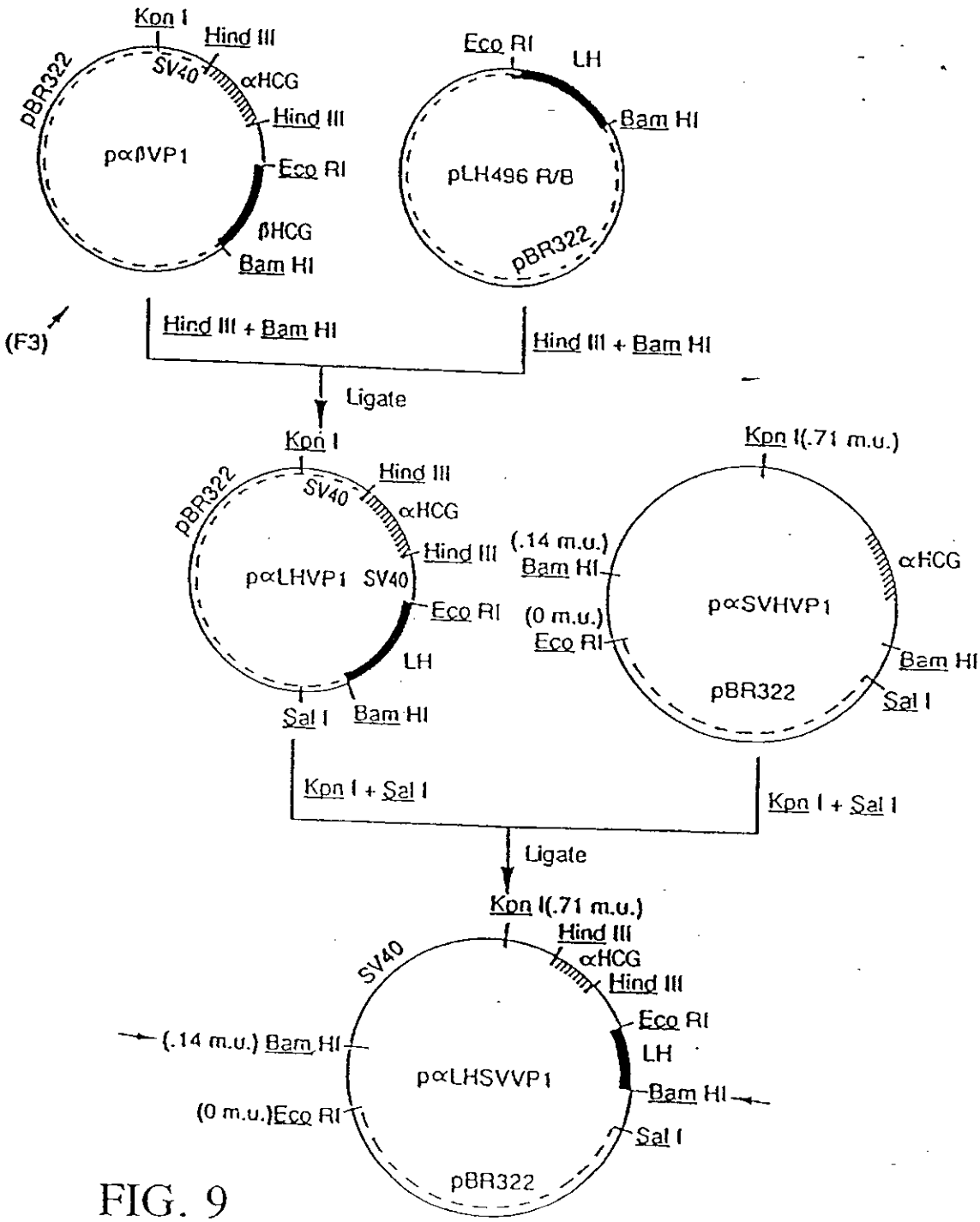

Kpn I
Hind III
SV40
αHCG
Hind III
Eco RI
βHCG
Bam HI
pBR322
pαβVP1
(F3)
Eco RI
LH
Bam HI
pLH496 R/B
pBR322
Hind III + Bam HI
Hind III + Bam HI
Ligate
Kpn I
Hind III
SV40
αHCG
Hind III
Eco RI
LH
Sal I
Bam HI
pBR322
pαLHVP1 SV40
Kpn I(.71 m.u.)
(.14 m.u.)
Bam HI
(0 m.u.)
Eco RI
αHCG
Bam HI
Sal I
pBR322
pαSVHVP1
Kpn I + Sal I
Kpn I + Sal I
Ligate
Kpn I(.71 m.u.)
Hind III
αHCG
Hind III
Eco RI
LH
Bam HI
Sal I
SV40
(.14 m.u.) Bam HI
(0 m.u.)Eco RI
pBR322
pαLHSVVP1

FIG. 9

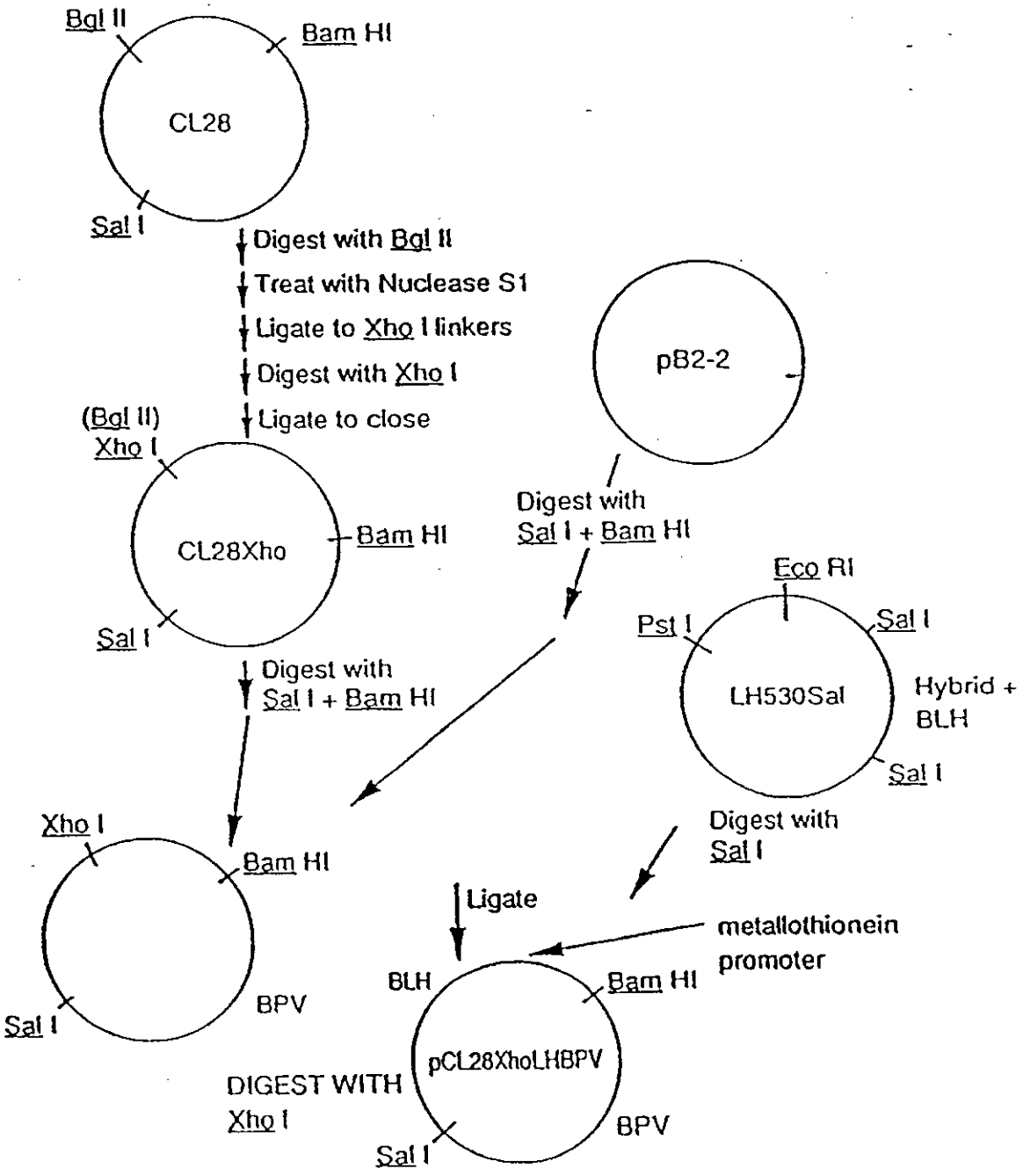

Bgl II
Bam HI
CL28
Sal I
Digest with Bgl II
Treat with Nuclease S1
Ligate to Xho I linkers
Digest with Xho I
Ligate to close
(Bgl II)
Xho I
CL28Xho
Bam HI
Sal I
pB2-2
Digest with
Sal I + Bam HI
Eco RI
Pst I
Sal I
LH530Sal
Hybrid +
BLH
Sal I
Digest with
Sal I + Bam HI
Digest with
Sal I
Xho I
Bam HI
Sal I
BPV
Ligate
metallothionein
promoter
BLH
Bam HI
pCL28XhoLHBPV
DIGEST WITH
Xho I
Sal I
BPV

FIG. 10

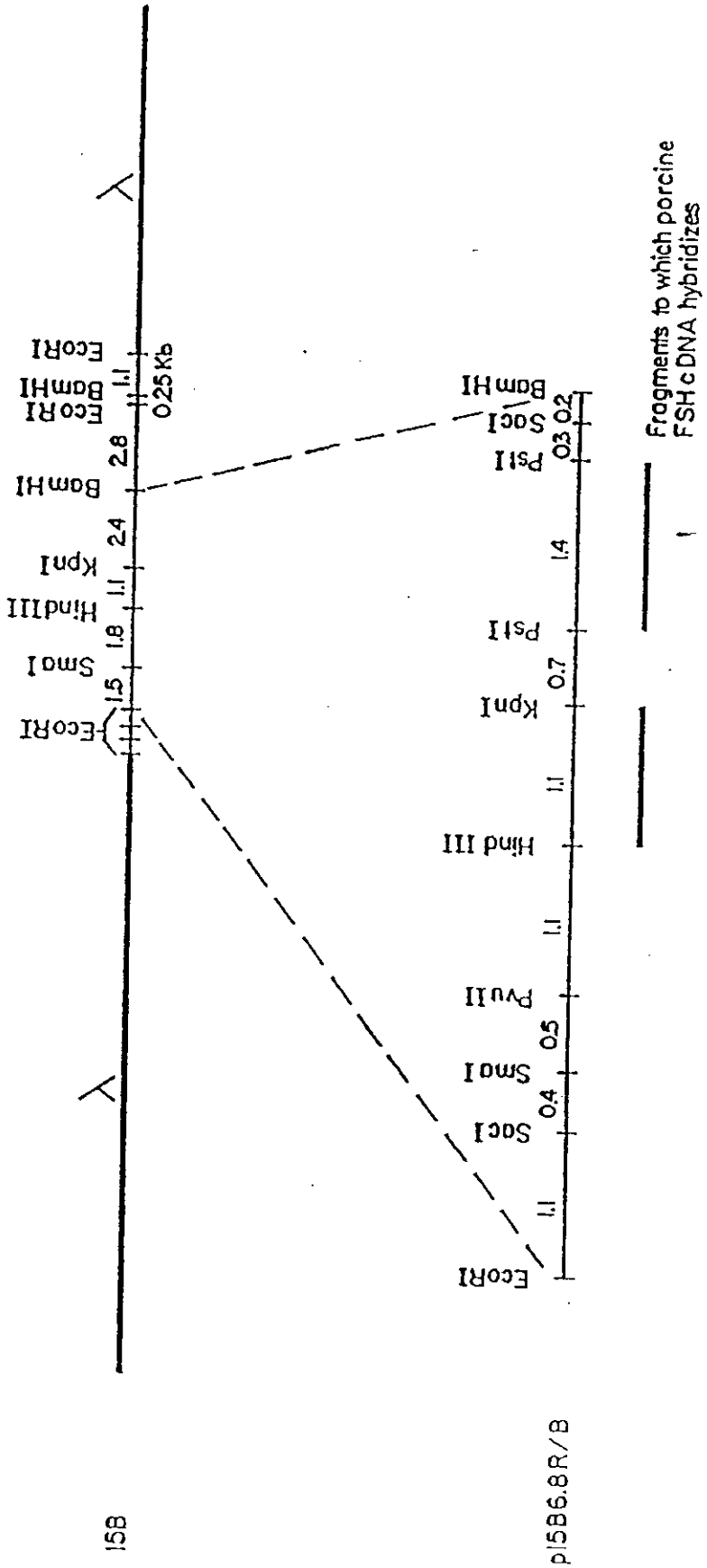

EcoRI
BamHI
EcoRI
BamHI
0.25Kb
1.1
2.8
BamHI
2.4
KpnI
1.1
HindIII
1.8
SmaI
1.5
EcoRI
BamHI
SacI
0.2
PstI
0.3
1.4
PstI
KpnI
0.7
1.1
HindIII
1.1
PvuII
0.5
SmaI
0.4
SacI
1.1
EcoRI
Fragments to which porcine FSH c DNA hybridizes
15B
p15B6.8R/B

FIG. 11

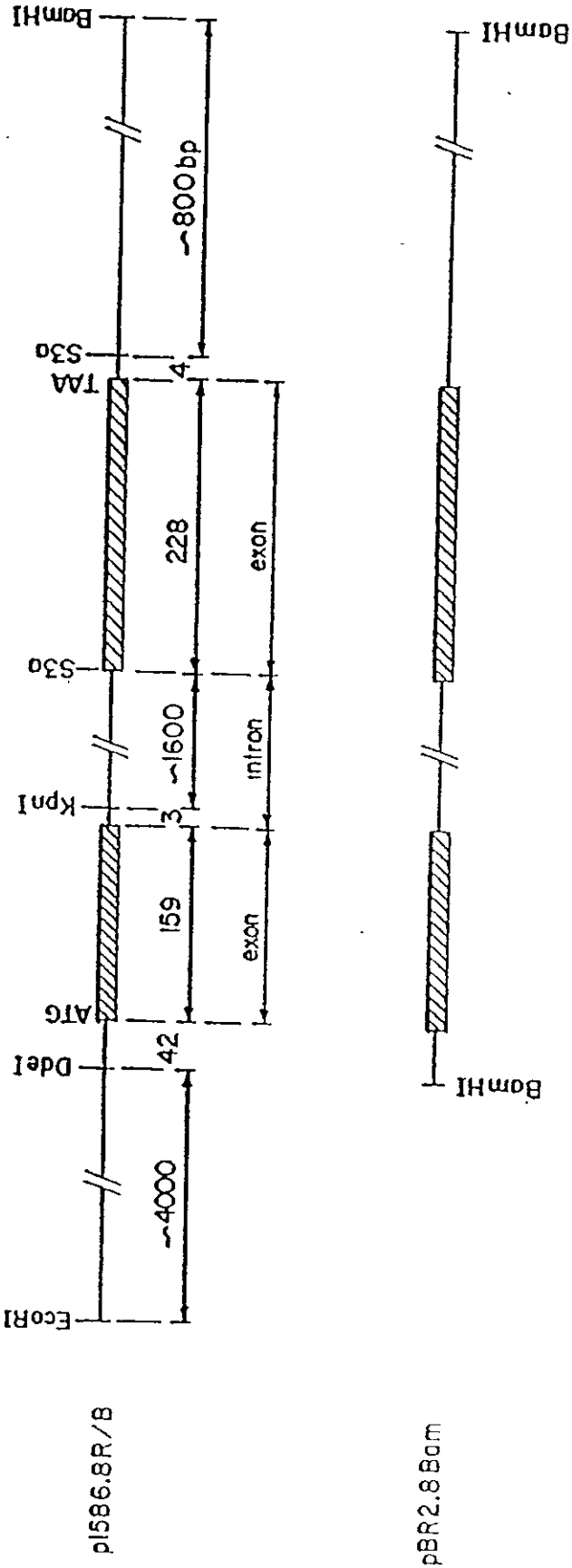

BamHI
~800bp
S3o
TAA
4
228
exon
S3o
~1600
intron
KpnI
3
159
exon
ATG
DdeI
42
~4000
EcoRI
p1586.8R/B
BamHI
BamHI
pBR2.8Bam

FIG. 12

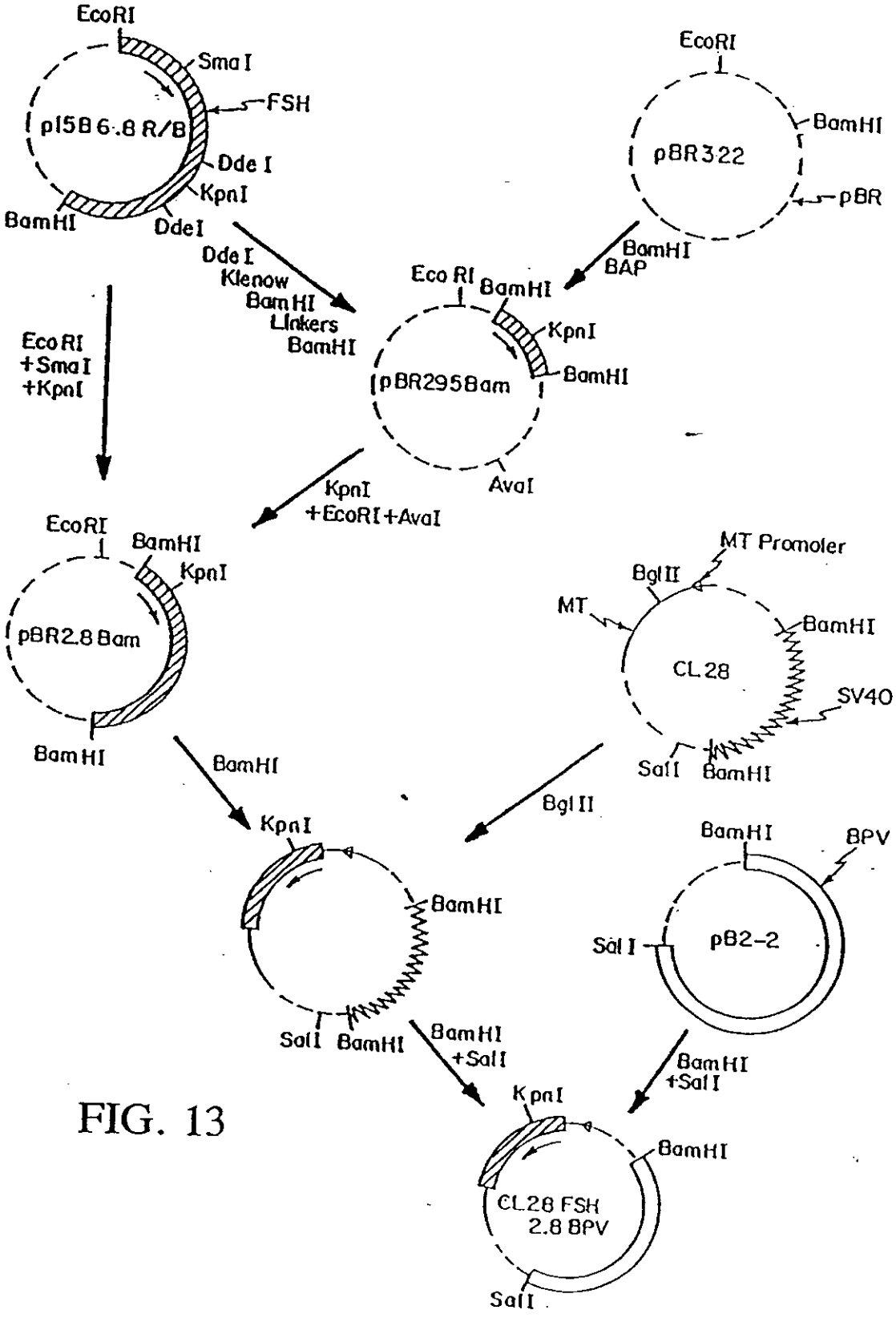

EcoRI
SmaI
FSH
pI586.8 R/B
DdeI
KpnI
BamHI
DdeI
DdeI
Klenow
BamHI
Linkers
BamHI
EcoRI
BamHI
pBR322
pBR
BamHI
BAP
EcoRI
+SmaI
+KpnI
Eco RI
BamHI
KpnI
pBR295Bam
BamHI
AvaI
KpnI
+EcoRI+AvaI
EcoRI
BamHI
KpnI
pBR2.8 Bam
BamHI
MT Promoter
BglII
MT
BamHI
CL28
SV40
SalI
BamHI
BamHI
BglII
KpnI
BamHI
SalI
BamHI
BamHI
BPV
SalI
pB2-2
BamHI
+SalI
BamHI
+SalI
KpnI
BamHI
CL28 FSH
2.8 BPV
SalI

FIG. 13

RECOMBINANT HETERODIMERIC HUMAN FERTILITY HORMONES, AND METHODS, CELLS, AND VECTORS AND DNA FOR THE PRODUCTION THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a division of U.S. application Ser. No. 07/515,481, filed Apr. 27, 1990, now abandoned, which is continuation-in-part of both Ser. No. 07/323,772, filed Mar. 15, 1989, now abandoned, and Ser. No. 06/696,647, filed Jan. 30, 1985, now U.S. Pat. No. 4,923,805 the entire contents of both of which are hereby incorporated herein by reference; Ser. No. 07/323,772 is a continuation of Ser. No. 06/548,228, filed Nov. 2, 1983, now U.S. Pat. No. 4,840,896; Ser. No. 06/696,647 is a continuation-in-part of said Ser. No. 06/548,228.

BACKGROUND OF THE INVENTION

The present invention relates to the use of recombinant DNA techniques to produce heterodimeric human fertility hormones.

Various polypeptide chains have been expressed, via recombinant DNA technology, in host cells such as bacteria, yeast, and cultured mammalian cells. Fiddes, J. C. and Goodman, H. M. *Nature*, vol. 281, pp. 351–356 (1979) and Fiddes, J. C. and Goodman, H. M., *Nature*, vol. 286, pp. 684–687 (1980) describe the cloning of, respectively, the alpha and beta subunits of human choriogonadotropin (hCG).

Sugimoto U.S. Pat. Nos. 4,383,034, 4,383,035 and 4,383,036 describe processes for producing FSH, LH and hCG, respectively, in which human lymphoblastoid cells are implanted into a laboratory animal, harvested from the animal, and cultured in vitro; accumulated hormone is then harvested from the culture. This technique is not capable of producing substantially pure hormone free of any other human fertility hormone.

Cohen et al, U.S. Pat. No. 4,468,464 mentions the production of fertility hormones by recombinant DNA techniques. However, Cohen et al only uses a prokaryotic system which cannot produce biologically active human fertility hormone.

Pierce et al, *Ann. Rev. Biochem.*, 50, 465–95 (1981) states that the alpha and beta subunits of LH are known to associate in vitro. The subunits referred to in this paper are obtained by dissociating naturally occurring dimeric hormone and allowing the units to reassociate. Such a disclosure does not permit the prediction that when synthesized by non-specialized cells transformed with recombinant DNA, the subunits would be properly glycosylated and folded for association so as to produce a biologically active hormone.

While many human proteins have been produced by recombinant DNA techniques the production of biologically active heterodimeric hormones by such techniques has not heretofore been accomplished. Heterodimeric fertility hormones are produced in the human body by highly specialized, differentiated cells which have evolved over a long period of time to carry out the specialized formation of producing each particular hormone. The mechanism by which post-translational heterodimeric assembly occurs intracellularly in these differentiated cells is not known, but it is known that proper assembly is necessary for biological activity. Undifferentiated cells do not, as far as is known, normally produce hormones. Thus, whether or not a biologically active heterodimeric hormone could be produced in undifferentiated cells transformed with DNA encoding the alpha and beta subunits was totally unpredictable.

SUMMARY OF THE INVENTION

The present invention stems from the unpredictable discovery that biologically active heterodimeric human fertility hormones can be produced in eukaryotic cells transformed by vectors containing the alpha and beta subunits of the hormone controlled by separate promoters. While alpha and beta subunits produced in separate cultures will not reassociate to form biologically active hormones, it has unexpectedly been discovered that when both subunits are produced in the same cell, a hormone is expressed which is biologically active.

Thus, the present invention includes the substantially pure heterodimeric human fertility hormones which can now be made totally free of other fertility hormones as well as any other human proteins. It also includes the process for production of such hormones, eukaryotic cells which have been transformed to so produce the hormones and vectors containing the DNA of both the alpha and beta subunits.

The present invention also includes the DNA encoding the beta subunits of hLH and hFSH, including cDNA coding for the beta subunit of human FSH, expression vectors containing such DNA and cells transfected therewith. The invention also includes DNA derivatives according to the genetic code which on expression code for the beta subunit of human FSH according to the present invention. The polypeptide structure of the beta subunit of hFSH has never before been accurately set forth.

Thus, in general, the present invention features, in one aspect, a substantially pure heterodimeric human fertility hormone composed of two different subunits and the process for the production thereof by means of which the two subunits are synthesized by single cell line, each cell having been transformed by an expression vector containing heterologous DNA encoding both subunits under control of separate promoters or two expression vectors each containing heterologous DNA encoding the separate subunits. The cell line is composed of eukaryotic cells which permit appropriate post-translational modification of the subunits such that the formed protein is biologically active. Because of the recombinant DNA technique which is used, the hormones produced are substantially pure and free of any other fertility hormones or any other human proteins. The preferred fertility hormones which are produced in accordance with the present invention are hCG, luteinizing hormone (LH) and follicle stimulating hormone (FSH).

In another aspect, the present invention features a cell transformed by at least one expression vector, which cell is capable of producing a biologically active heterodimeric protein that is encoded at least in part by the vector. In preferred embodiments: a second expression vector encodes a second portion of the protein or at least two subunits of the protein are encoded by a single expression vector; the vectors are autonomously replicating, preferably a replicating virus or a plasmid; the cell is a mammalian cell, such as a monkey or mouse cell; transcription of the different subunits is under the control of the SV40 late promoter; transcription of the alpha subunit of the protein is under the control of the SV40 early promoter and transcription of the beta subunit is under control of the mouse metallothionein promoter, or transcription of both subunits is under the control of the mouse metallothionein promoter; and the expression vector which includes the mouse metallothionein

promoter also includes at least the 69% transforming region of the bovine papilloma virus (BPV) genome.

In another aspect, the invention features an autonomously replicating expression vector including two genes encoding two different heterologous proteins, the genes being under the control of two different promoters, most preferably a metallothionein promoter and a BPV promoter; the use of different promoters advantageously minimizes the possibility of deleterious recombinations.

In a further aspect, the invention features the DNA for the beta subunits of hLH and hFSH.

As used herein, "subunit" refers to a portion of a protein, which portion, or homologue or analogue thereof, is encoded in nature by a distinct mRNA. Thus, for example, a heavy chain and a light chain of an IgG immunoglobulin are each considered a subunit. Insulin, on the other hand, is composed of two chains which are not considered subunits, because both are, in nature, encoded by a single mRNA, and cleavage into two chains naturally occurs only after translation.

The term "expression vector" refers to a cloning vector which includes heterologous (to the vector) DNA under the control of control sequences which permit expression in a host cell. Such vectors include replicating viruses, plasmids, and phages. Preferred vectors are those containing at least the 69% transforming region, and most preferably all, of the bovine papilloma virus genome.

The invention permits the production of a biologically active heterodimeric human fertility hormone from a single culture of transformed cells which hormone undergoes, in the culture, post-translational modification, e.g. glycosylation and proteolytic processing, for biological activity and stability.

In preferred embodiments, each expression vector is autonomously replicating, i.e., not integrated into the chromosome of the host cell. The use of autonomously replicating expression vectors prevents undesirable influence of the desired coding regions by control sequences in the host chromosome.

Other advantages and features of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

We turn now to the preferred embodiments of the invention, first briefly describing the drawings thereof.

FIG. 1 is a diagrammatic illustration of the construction of the plasmid p alpha SVHVP1, which contains the alpha hCG cDNA clone, portions of SV40 viral DNA, and sequences of the plasmid pBR322.

FIG. 2 is a diagrammatic illustration of the construction of plasmid p beta SVVP1, which incorporates the beta hCG cDNA clone, regions of SV40 DNA and a portion of pBR322 including the region conferring resistance to ampicillin on host *E. coli*.

FIGS. 3-3A is a diagrammatic illustration of the construction of the plasmid p alpha beta SVVP1 in which the alpha and beta hCG cDNA clones are inserted into SV40 DNA.

FIG. 4 is a diagrammatic illustration of the construction of the plasmids pRF375 and pRF398.

FIG. 5 is a diagrammatic illustration of the construction of the plasmid RF398 alpha t_2.

FIG. 6 is a diagram illustrating the location of an 88 bp probe within the beta hCG cDNA clone.

FIG. 7 illustrates the beta LH restriction map, and the pieces used in the construction shown in FIG. 8.

FIG. 8 is a diagrammatic illustration of the construction of a plasmid, LH520H/B, containing the complete mature beta LH cDNA clone.

FIG. 9 is a diagrammatic illustration of the construction of the viral vector p alpha LHSVVP1.

FIG. 10 is a diagrammatic illustration of the construction of the BPV-containing plasmid pCL28XhoLHBPV, encoding the beta subunit of LH.

FIG. 11 is a partial restriction map of the lambda clone 15B and the beta FSH-containing 6.8 kb EcoRI-BamHI fragment that is inserted into pBR322.

FIG. 12 is a partial restriction map of the beta FSH coding region and the BamHI fragment that is inserted into a BPV based expression vector.

FIG. 13 is a diagrammatic illustration of the construction of the BPV-containing plasmid CL28FSH2.8BPV, encoding the beta subunit of FSH.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENT

The cloning vectors of the invention have the general structure recited in the Summary of the Invention, above. Preferred vectors have the structures shown in the Figures, and are described in more detail below.

Construction of Cloning Vectors

Isolation of cDNA Clones Encoding the Alpha and Beta Subunits of hCG

All of the techniques used herein are described in detail in Maniatis et al, (1982) *Molecular Cloning: A Laboratory Manual* (Cold Spring Harbor Laboratory), hereby incorporated by reference.

RNA is extracted from placental tissue by the following method. Homogenization of the tissue is carried out in a 1:1 mixture of phenol:100 mM Na-acetate (pH 5.5) containing 1 mM EDTA, that has been warmed to 60° C. for 20 min. After cooling on ice for 10 min., the phases are separated by centrifugation. The hot phenol extraction is repeated twice more followed by two extractions with chloroform.

RNA is precipitated from the final aqueous phase by the addition of 2.5 volumes of ethanol.

In order to enrich for poly A^+ mRNA, placental RNA is passed over oligo (dT)-cellulose in 0.5M NaCl buffered with 10 mM Tris-HCl, pH 7.5, and washed with the same solution. Poly A^+ mRNA is eluted with 10 mM Tris-HCl (pH 7.5), 1 mM EDTA, 0.05% SDS and precipitated twice with ethanol. Typical initial yields are 1.5–2.0 mg of total RNA per g of tissue, of which about 2% is poly A^+ mRNA.

Placental cDNA libraries are constructed by reverse transcription of placental mRNA, second strand synthesis using *E. coli* DNA polymerase I (large fragment), treatment with S1 nuclease, and homopolymer tailing (dC) with terminal deoxynucleotidyl transferase; all such procedures are by conventional techniques.

In a typical preparation, 20–30% conversion of mRNA to single strand (ss) cDNA; 70% resistance to digestion with nuclease S1 after second strand synthesis; and dC "tails" of ten to twenty-five bases in length, are obtained. These cDNA molecules are then annealed to DNA fragments of the plasmid pBR322, which has been digested with PstI, and to which dG "tails" have been added. These recombinant plasmids are then used to transform *E. coli* cells to generate

a cDNA library (transformed cells are selected on the basis of tetracycline resistance).

In order to identify the human alpha hCG clone, a 219 bp fragment of a mouse alpha thyroid stimulating hormone (TSH) clone is used as a hybridization probe. This probe has 77% sequence homology with the human clone. It is radioactively labeled by nick translation and hybridized to the cDNA library under conditions that take into account the extent of homology. Strongly hybridizing clones are analysed by restriction mapping and clones containing the complete coding sequence of alpha hCG are verified by DNA sequencing.

Construction of Plasmid p alpha SVHVP1

Referring to FIG. 1, in order to construct the plasmid alpha 970 H/B, a cDNA clone containing the alpha hCG fragment is digested with NcoI. The NcoI site, just 5' to the ATG codon signalling initiation of translation, is filled in and ligated to a synthetic HindIII linker. Similarly, the natural HindIII site in the 3' untranslated region of the clone is cut, filled in with *E. coli* DNA polymerase Klenow, and then ligated to a synthetic BamHI linker. This fragment is cloned into the plasmid pBR322 between its HindIII and BamHI sites to generate the plasmid alpha 574 H/B. This plasmid is digested with BamHI, treated with alkaline phosphatase, and ligated to the 396 bp Sau3A fragment of SV40 DNA (from 0.07 to 0.14 map units) which has been isolated from a polyacrylamide gel. The ligation mix is used to transform *E. coli* to ampicillin resistance and the desired plasmid, alpha 970 H/B, is identified among the transformants.

The plasmid Q_27 is constructed by cutting SV40 at its HsaII site, making flush ends by digestion with nuclease S1, ligating on EcoRI linkers, digesting with EcoRI, and cloning the resulting 1436 bp fragment into the EcoRI site of pBR322.

Referring to FIG. 1, Q_27 is digested completely with EcoRI and partially with HindIII; the fragment from 0.72 to 0.94 map units is isolated and cloned into alpha 970 H/B, which has been digested with EcoRI and HindIII and treated with alkaline phosphatase. The ligation mix is used to transform *E. coli*, and the desired plasmid, p alpha SVL, is identified among the transformants by restriction mapping.

p alpha SVL is digested with EcoRI and the fragment of SV40, with EcoRI ends, extending from 0 to 0.72 map units, and containing the SV40 origin of replication and the intact early region, is ligated to it to generate the plasmid p alpha SVHVP1, which is isolated from *E. coli* transformants.

Construction of Plasmid p beta SVVP1

A 579 bp cDNA clone coding for beta hCG was obtained from John C. Fiddes at Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. (Fiddes et al, *Nature*, vol. 286, pp. 684–687 (1980)). This fragment is ligated at each end to synthetic BamHI linkers. After digestion by HqaI restriction enzyme, the ends are filled in with Klenow DNA polymerase and synthetic EcoRI linkers are ligated on so that an EcoRI site is about 10 bp 5' to the ATG codon of the signal peptide coding sequence. A BamHI site is about 60 bp 3' to the nonsense codon marking the end of the coding sequence. Referring to FIG. 2, this 556 bp. EcoRI-BamHI fragment is isolated and cloned into pBR322, between the EcoRI and BamHI sites, to give the plasmid p beta 556 R/B.

In order to construct the plasmid PSVHR (FIG. 2), SV40 DNA is partially digested with HindIII to yield linear molecules, digested with nuclease S1 to make flush ends, ligated to synthetic EcoRI linkers and digested with EcoRI and BamHI. The fragment from 0.94 to 0.14 map units, containing the SV40 origin of replication and early region, is cloned into pBR322 as an EcoRI-BamHI piece.

Referring still to FIG. 2, the EcoRI site of the plasmid p beta 556 R/B is methylated in a reaction catalyzed by EcoRI methylase, following which the plasmid is cut with NdeI. EcoRI linkers are ligated to the S1 treated NdeI flush ends and activated by digestion with EcoRI, which is followed by digestion with BamHI.

The SV40 fragment of pSVHR from the EcoRI site to the BamHI site is isolated and ligated in a reaction mix containing the digestion fragments of p beta 556 R/B. Following ligation, the mix is digested with SalI to eliminate plasmids which have re-inserted the EcoRI (NdeI) to BamHI piece of pBR322. *E. coli* is transformed with the digested ligation mix and p beta SVVP1 is identified and isolated.

Construction of the Plasmid p Alpha Beta SVVP1

Referring to FIGS. 3–3A, pBR322/Kpn is derived from pBR322 by inserting a KPnI linker into its unique EcoRI site, after this site is deleted by digestion with EcoRI, followed by digestion with S1 nuclease.

Referring still to FIGS. 3–3A, SV40 DNA is digested with AvaII. The staggered ends of the resulting fragments are filled in by Klenow DNA polymerase to form flush ends, and the mixture is then fractionated on a polyacrylamide gel. The 682 base pair fragment (0.64 to 0.77 map units) containing the origin of replication and the unique KpnI site is isolated from the gel, ligated to synthetic HindIII linkers, and digested with HindIII and KsnI.

The resulting fragments are ligated to pBR322/Kpn. p266, which contains the 266 base pair KpnI HindIII fragment, including the SV40 late promoter region, is isolated. p266 is cut with HindIII and BamHI, and treated with bacterial alkaline phosphatase.

Still referring to FIGS. 3–3A, p beta SVVPI/B is constructed as follows: p beta SVVPI (FIG. 2) is cut with EcoRI, followed by ligation to eliminate pBR322 sequences. Subsequently, this DNA is cut with BamHI and cloned into the BamHI site of pBR322.

The resulting plasmid, p beta SVVPI/B, is then digested with HindIII and BamHI and the 1003 base pair HindIII-BamHI fragment is ligated into p266 to yield the plasmid p beta VP1 266, in which the beta hCG cDNA is positioned downstream from the SV40 late promoter in such a way that its RNA transcript would be spliced as if it were the viral VP1 transcript.

The alpha hCG cDNA is inserted into p beta VP1 266 as a HindIII fragment, which has been cut at its HindIII site and treated with bacterial alkaline phosphatase. *E. coli* transformants derived from this ligation are screened by restriction mapping, and plasmids are isolated that have the desired structure, in which the alpha hCG cDNA has replaced VP2 in the correct orientation, followed downstream by the beta hCG cDNA, which has replaced VP1.

One such isolated plasmid, p alpha beta VP1, is used to complete the construction of p alpha beta SVVP1. The plasmid is cut with KPnI, and the full SV40 genome, cut with KpnI, is inserted by ligation into this site. Following transformation of *E. coli*, a plasmid with the required structure, p alpha beta SVVP1, is isolated. This plasmid contains DNA encoding both the alpha and beta subunits of hCG, and thus is capable of directing the expression, in host mammalian cells, of both subunits, whereby biologically

functional, glycosylated heterodimeric hCG is produced (glycosylation occurs post-translationally).

Construction of Plasmids pRF 375 and pRF 398

Referring to FIG. 4, the plasmid CL28 (identical to plasmid JYMMT(B); Hamer et al., *J. Mol. Applied Gen.*, 1, 273–288 (1983)), containing the murine metallothionein promoter, SV40 DNA, and pBR322 sequences, is cut with the restriction endonuclease Bgl II. At this site are inserted cDNA clones of either alpha hCG or beta hCG, containing untranslated regions of about 10 and 30 bp at their 5' and of about 220 and 60 bp at their 3' ends. These clones have been genetically engineered by the addition of synthetic BamHI linkers at their termini.

The resulting plasmids pRF 302 (alpha) or pRF 394 (beta) are digested with restriction enzymes BamHI and SalI to release the SV40 DNA sequences.

Plasmid pB2-2, which contains the entire BPV genome, and some pBR322 sequences, is digested with BamHI and SalI to yield the BPV genome with BamHI/SalI ends; this fragment is ligated into pRF 302 (alpha) and pRF 394 (beta) containing the metallothionein-hCG sequences.

Following transformation of *E. coli*, plasmids pRF 375 and pRF 398 are identified and isolated. They encode alpha hCG or beta hCG, respectively, under the control of the mouse metallothionein promoter.

Construction of the Plasmid RF 398 alpha t_2

Referring to FIG. 5, the plasmid p alpha t_2 is derived by cloning the alpha hCG 574 HindIII fragment into plasmid pVBt2 (V. B. Reddy et al., *PNAS*, 79, 2064–2067, 1982). p alpha t_2, which contains the alpha hCG cDNA under the control of the SV40 early promoter, is digested with EcoRI. The 5' overhangs are removed by S1 nuclease digestion prior to the addition of synthetic BamHI linkers by blunt end ligation.

Plasmid RF 398 (FIG. 4) is digested with BamHI and treated with bacterial alkaline phosphatase. The 1735 base pair BamHI fragment of p alpha t_2 is inserted in to RF 398. The resulting plasmid RF 398 alpha t_2 is isolated from *E. coli* transformants. This plasmid thus has the beta hCG cDNA in a transcriptional unit under control of the mouse metallothionein promoter and the alpha hCG cDNA in a transcriptional unit controlled by the SV40 early promoter.

Expression of Luteinizing Hormone (LH) cDNA Clones Construction of a Human Pituitary cDNA Library

RNA is prepared from human pituitaries by homogenizing 5 to 10 grams of the frozen glands in 20 ml of a solution containing 4M guanidine thiocyanate, 1M 2-mercaptoethanol, 0.05M Na-acetate (pH 5.0), and 0.001M EDTA. One g CsCl is added per ml of homogenate and the suspension is centrifuged at 2,000 rpm for 15 min. The supernatant is layered carefully over a 15 ml cushion of CsCl solution (containing 1.25 ml of 1M Na-acetate (pH 5), 62.5 microliters of 0.4M EDTA and 39.8 g of CsCl in a final volume of 35 ml) and centrifuged at 45,000 rpm in the Ti 70 rotor of a Beckman ultracentrifuge for 18–24 h at 20° C. The RNA visible as a pellicle in the gradient is removed with a syringe, diluted, and precipitated by the addition of two volumes of ethanol. Following three cycles of dissolution and reprecipitation, the RNA pellet is dissolved in H_2O and brought to 0.01M Tris-HCl (pH 7.5) and 0.5M NaCl by the addition of concentrated stock solutions. The preparation is then enriched for poly A^+ mRNA by two passes over oligo dT-cellulose, as described above in the case of placental RNA.

A human pituitary cDNA library is constructed from the poly A^+ mRNA as described above for placental poly A^+ mRNA except that both the large fragment *E. coli* DNA polymerase I and the avian myeloblastosis virus reverse transcriptase are used sequentially for second strand cDNA synthesis. Reverse transcriptase is used first. The reaction is stopped by phenol extraction. The aqueous phase of the centrifuged extract is applied to a 5 ml column of BioGel A-5m. Fractions containing high molecular weight material are pooled, concentrated, precipitated with two volumes of ethanol, dried, and dissolved in 100 mM Tris-HCl (pH 8.3), 10 mM $MgCl_2$, 140 mM KCl, 20 mM 2-mercaptoethanol, 1 mM of each of the four deoxyribonucleoside triphosphates, for reverse transcription. Reverse transcriptase is added to about 20 units per microgram of cDNA. Double stranded cDNA is then treated with nuclease S1, tailed, and cloned as described above.

Isolation of Beta LH cDNA Clones

Colonies grown on nutrient agar plates containing 25 micrograms per ml of tetracycline are transferred to nitrocellulose filters. Colonies are lysed in situ by treatment with 0.5M NaOH and neutralized with 0.5M Tris-HCl (pH 7.4) containing 1.5M NaCl. Liberated DNA is fixed to the filter by baking at 80° C. in a vacuum oven for 2 h. The filters are screened by hybridization to a ^{32}P labeled 88 base pair fragment of the beta hCG clone corresponding to amino acids 16 to 45 of the mature hCG beta chain, which has 29 of 30 amino acids in common with this region of the beta LH polypeptide (FIG. 6). Hybridization is carried out overnight at 32° C. in 50% formamide, 0.75M NaCl, 0.075M Na-citrate (pH 7.0), 2.5% dextran sulfate, 0.1% polyvinylpyrollidone, 0.1 mg per ml bovine serum albumin, and at least 10^5 cpm per filter of ^{32}P-labeled 88 bp beta hCG fragment. Filters are washed several times in 0.15M NaCl, 0.015M Na-citrate at 37° C. before autoradiography. One of the positive isolated clones LH12 (FIG. 7), is used further. LH12 is 365 bp long and includes sequences coding for 15 amino acids of the pre-beta signal sequence plus 105 amino acids of the mature beta LH polypeptide. Its nucleotide sequence is determined. Since the complete mature beta LH is not coded by LH12, further screening of the human pituitary cDNA library is carried out using a 240 bp NcoI-PvuII fragment of LH12 (FIG. 7) as a ^{32}P labeled hybridization probe. The clone LH6 (FIG. 7) is isolated from this screening. LH6 contains the complete 3' end of beta LH, including the region corresponding to the untranslated portion of the mRNA through 27 A residues of the poly A "tail" of the mRNA. No clones are found that extended further than LH12 in the 5' direction. DNA sequencing of the complete, combined mature beta LH coding regions reveals two differences in the amino acid sequence of beta LH from the published protein sequence data: position 42 is a methionine and position 55 is a valine. Also, the mature beta LH contains 121 amino acids, based on the cDNA sequence.

A clone containing an intact signal peptide coding sequence and the complete mature beta LH sequence is constructed as shown in FIG. 8, using the restriction fragments illustrated in FIG. 7. A 104 bp EcoRI-DdeI fragment is isolated from the plasmid beta 579 H and ligated to an isolated 181 bp DdeI fragment, subsequently digested with PstI, from the LH12 plasmid. Following ligation overnight at 15° C., the ligation mix is digested with EcoRI and PstI and fractionated on a 7% polyacrylamide gel from which the

desired 256 bp fragment is isolated. This fragment fuses the beta hCG signal sequence to that of the pre-beta LH in such a way as to provide a coding sequence for a 20 amino acid signal peptide.

The 256 bp EcoRI-PstI fragment is cloned into pBR322 digested with EcoRI and PstI so as to give the plasmid LH beta 260. The 146 bp EcoRI-NcoI fragment indicated in FIG. 8 is isolated from a polyacrylamide gel and used later in the construction as described below.

The LH6 plasmid (FIG. 8) is digested with Sau3a and the 390 bp fragment is isolated by polyacrylamide gel electrophoresis. This fragment is then digested with HincII, ligated to BamHI linkers, digested with BamHI, and cloned into the plasmid pAPP at the BamHI site. pAPP is derived from pBR322 by digestion with AvaI, filling in the 5' overhang with the dNTP's and the large fragment DNA polymerase I of *E. coli*, digestion with PvuII, and ligation to close the plasmid so as to eliminate the PvuII site. The plasmid BH6B, isolated from the ligation of the 340 bp BamHI fragment into the BamHI site of pAPP, is digested with EcoRI and PvuII, and treated with bacterial alkaline phosphatase. The fragments are ligated to a mixture of the 145 bp EcoRI-NcoI fragment of LH beta 260, described above, and the isolated 241 bp NcoI-PvuII fragment from the plasmid LH12 shown in FIG. 8. The ligation mix is used to transform *E. coli* to ampicillin resistance. The plasmid LH 520 H/B is found among the transformants. LH 520 H/B contains a complete beta LH coding sequence including a hybrid signal peptide sequence.

Construction of p Alpha LHSVVP1

In order to express this pre-beta LH clone in an SV40-based vector, as had been done for the pre-alpha and pre-beta hCG clones described previously, it is desirable to place an EcoRI site very close to the ATG of the pre-beta coding sequence. This is accomplished by digesting LH520 H/B with HgaI, filling in the 5' overhang, ligating on synthetic EcoRI linkers, digesting with EcoRI and BamHI, and cloning the isolated 496 bp EcoRI-BamHI fragment into pBR322 digested with EcoRI and BamHI and treated with bacterial alkaline phosphatase. The plasmid pLH496 R/B is isolated from *E. coli* transformed with this ligation mix and is used as the source of the 496 bp fragment to be expressed.

The plasmid p alpha beta VP1, whose construction and use in expressing both subunits of hCG is described earlier (FIG. 3), is digested with EcoRI and BamHI and ligated in a reaction mix containing the plasmid pLH496 R/B which had been digested with both of these enzymes (FIG. 9). The plasmid p alpha LHVP1 is identified among the *E. coli* transformants. As shown in FIG. 9, the intact SV40 viral early region is taken from p alpha 8VHVP1 (FIG. 1) and inserted by ligation as a KsnI-SalI fragment into p alpha LHVP1 which had been digested with KsnI and SalI to give the plasmid p alpha LHSVVP1. By cutting this plasmid with BamHI and religating, the virus alpha LHSVVP1 is formed. This virus contains cloned cDNA's for the common (to LH and hCG, as well as FSH and TSH) alpha subunit and the specific beta LH subunit under control of the SV40 late promoter. The cloned cDNA's are positioned in such a way that the common alpha insert replaced the viral VP1 protein coding sequence and the beta LH insert replaced the viral VP2 coding sequence.

Insertion of the Beta LH cDNA (With Beta hCG 5' End of Signal Peptide) into a BPV-Based Expression System

LH 520 H/B (FIG. 8) is digested with HindIII and BamHI, treated with the *E. coli* DNA polymerase (Klenow), ligated to synthetic SalI linkers, digested with SalI, and cloned into the SalI site of pBR322. The resulting plasmid, LH 530 Sal, is used as a source of the LH cDNA clone for insertion into the mouse metallothionein gene of the plasmid CL28 as described in FIG. 10.

CL28 is cut with BsIII, treated with nuclease S1, and ligated to XhoI linkers. Following digestion with XhoI, ligation and digestion with BsIII, *E. coli* is transformed with the reaction mix to give the plasmid CL28Xho. This plasmid is digested with BamHI and SalI and ligated to a BamHI plus SalI digest of the plasmid pB2-2 (FIG. 4) to give the plasmid CL28XhoBPV. The latter LH insert is then ligated into the XhoI site of CL28XhoBPV as a SalI fragment, since the 5' overhang of SalI digests is complementary to that of XhoI digests. Following digestion with XhoI to eliminate background, *E. coli* is transformed and the desired plasmid pCL28XhoLHBVP containing the (hybrid) pre-beta LH insert, in a BPV-based plasmid, under control of the mouse metallothionein promoter, is isolated.

Transfection and Infection of Host Monkey Cells

The incorporation of virus-containing vectors into eukaryotic cells for the production of a heteropolymeric protein is generally accomplished as follows. First, if the viral DNA and homopolymeric protein-encoding DNA are incorporated into a plasmid, which is maintained, in, say, *E. coli*. the plasmid sequences (e.g. the pBR322 sequences) are removed and the resulting DNA is ligated to form circular DNA including the viral region and the heteropolymeric protein-encoding sequence or sequences. This circular DNA generally does not contain all of the genetic information needed to produce a replicating virus, the other necessary sequences (e.g. those encoding coat protein) having been replaced by the heteropolymeric protein-encoding sequence or sequences. The circular DNA, minus the plasmid DNA, must be close enough in size to the naturally occurring viral DNA from which it is derived to permit the DNA to enter and replicate in appropriate host mammalian cells.

The circular DNA is used to transfect host cells in order to produce virus stock for later infections. Since some of the DNA necessary to produce virus is missing, the transfection must occur in conjunction with helper virus DNA encoding enough of the missing function to produce replicating virus.

Transfected host cells are grown and incubated until lysed by replicating virus. The resulting replicating virus stock, including helper virus, is then used to infect host cells for production of the heteropolymeric protein. Virus stock is maintained, since it generally needs to be reused to infect fresh batches of host cells, as each culture of infected, protein-producing host cells generally is eventually lysed by the virus.

The specific recombinant DNA sequences described above are used to transfect, and then infect, host cells, as follows.

The pBR322 sequences are removed from the above-described SV40-containing plasmids to produce transfecting viral DNA. In the case of p alpha SVHVP1 and p alpha beta SVVP1, this is accomplished by digestion with BamHI, followed by ligation under conditions favoring circularization of the fragments to give (among other products) alpha SVHVP1 and alpha beta SVVP1. For p beta 8VVP1, digestion with EcoRI followed by re-ligation brings the SV40 late promoter and VP1 splice region into juxtaposition with the beta hCG cDNA insert at the same time that it eliminates pBR322 sequences and forms beta SVP1. At the same time, PtsA58 Bam (tsA58 SV40 viral DNA cloned into the

pBR322 BamHI site) is cut with BamHI and ligated to obtain self-ligated circles. Analogous methods are used for the LH vectors. Separate virus stocks are prepared as described below.

The DNA's, which are cut and ligated as described above, are ethanol precipitated and dissolved in sterile water. Approximately 1 μg of ptsA58 Bam DNA (helper virus) and 10 μg of recombinant DNA (encoding alpha and/or beta hCG or LH) are combined in a sterile test tube, mixed with 2 ml of TBS buffer (G. Kimura and R. Dulbecco 1972, Virology, 49, 79–81) and 1 ml of 2 mg/ml DEAE-dextran solution and added to a monolayer of confluent monkey CV-1 cells previously washed twice with 10 ml of TBS in a T-75 flask. The cells are left at 37° C. for 1–2 hrs with occasional shaking, washed with TBS twice, fed with 10 ml of DMEM containing 5% fetal calf serum, and left at 40° C. for 10–15 days. After complete cell lysis, the medium is transferred to a test tube, frozen and thawed five times, and centrifuged at 3000 rpm for five minutes. The resulting supernatants serve as virus stocks for infection of fresh CV-1 cells.

To accomplish an infection, CV-1 cells are grown to confluence in a T-150 flask. 1 ml of one of the virus stocks (made as described above) is added to the flask and the cells are incubated at 40° C. for 5 days.

For mixed infections, CV-1 cells are grown to confluence in a T-150 flask, alpha SVHVP1 and beta SVVI viruses are mixed in a 1:1 ratio and 1 ml of the mixed virus is used to infect CV-1 cells at 40° C.

Transfection of Mouse Cells

To produce heterodimeric hCG using a mixed transfection, five μg of each BPV plasmid, i.e., pRF 375 (alpha hCG) and pRF 398 (beta hCG), are mixed and added to 0.5 ml of a 250 mM $CaCl_2$ solution containing 10 μg of salmon sperm DNA as carrier. This mixture is bubbled into 0.5 ml of 280 mM NaCl, 50 mM Hepes and 1.5 mM sodium phosphate. The calcium phosphate precipitate is allowed to form for 30–40 minutes at room temperature.

24 hours prior to transfection, 5×10^5 cells of mouse C127 cells (available from Dr. Dean Hamer, National Cancer Institute, NIH, Bethesda, Md.) are placed in a 100 mm dish or T-75 flask. Immediately before adding the exogenous DNA, the cells are fed with fresh medium (Dulbecco's Modified Medium, 10% fetal calf serum). One ml of calcium phosphate precipitate is added to each dish (10 ml), and the cells are incubated for 6–8 hours at 37° C.

The medium is aspirated and replaced with 5 ml of 20% glycerol in phosphate buffered saline, pH 7.0 (PBS) for 2 minutes at room temperature. The cells are washed with PBS, fed with 10 ml of medium, and incubated at 37° C. After 20–24 hours, the medium is changed and subsequent refeeding of the cells is carried out every 3–4 days. Individual clones are grown in T-25 cm flasks. After 7–21 days, cell clones can be transferred to larger flasks for analysis.

To produce heterodimeric hCG using a single transfection, plasmid RF 398 alpha t_2 is employed in the same manner as the above two plasmids were employed for a mixed infection.

To make heterodimeric LH, plasmids pRF 375 and pCL28XhoLHBPV are mixed, as described above in the case of hCG.

An interesting observation is that culturing cells containing beta hCG or beta LH-encoding vectors alone, in the absence of alpha-encoding cells, produces practically no beta subunit, while cells containing alpha and beta-encoding sequences produce not only heterodimer, but free beta subunit as well. This leads support to the notion that the production of both subunits in a single cell culture has the additional advantage of somehow permitting the presence of the alpha subunit to stabilize the beta subunit.

A further interesting observation was that mouse C127 cells transformed by an expression vector for the alpha subunit of hCG, without the additional vector for the beta subunit, produces an alpha subunit which will not associate with the complementary urinary beta subunit (combination<5%). The recombinant alpha subunit apparently has more glycosylations than the native subunit and is thus prevented from combining with beta subunit to produce a biologically active hormone. However, when both subunits are produced by the same cells, proper association and glycosylation occurs in vivo so that biologically active hormone substantially identical to the native hormone is expressed.

Isolation of the Human Beta FSH Gene

A human genomic library in phage lambda (Lawn et al., *Cell*, 15, 1157–1174 (1978)) is screened using "guessed" long probes. The idea behind such probes, set forth in Jaye et al., *Nucleic Acids Research*, 11, 2325 (1983), is that if the amino acid sequence of a desired protein is at least partially known, a long probe can be constructed in which educated guesses are made as to the triplet encoding any amino acid which can be encoded by more than one, and not more than four, different triplets. Any correct guesses increase the amount of homology, and improve the specificity, of the results.

To isolate desired regions of DNA, two labeled 45-mer probes are used: TB36. homologous with amino acids 56-70 of human beta FSH; and TB21, homologous with amino acids 73-87. These probes have the following nucleotide compositions (corresponding amino acids are also given):

TB36:
(AA56-70) 3'

Val—Tyr—Glu—Thr—Val—Lys—Val—
CAC ATG CTC TGG CAC TCT CAC

Pro—Gly—Cys—Ala—His—His—Ala—Asp
GGT CCG ACG CGG GTG GTG CGA CTG 5'

TB21:
(AA73-87) 3'

Tyr—Thr—Tyr—Pro—Val—Ala—Thr—
ATG TGC ATG GGT CAC CGA TGT

Glu—Cys—His—Cys—Gly—Lys—Cys—Asp
CTC ACA GTG ACG CCG TTT ACG CTG 5'

The above probes are used to screen the human genomic library as follows. TB21 is labeled with ^{32}P and used to screen approximately 5×10^5 lambda plaques on duplicate filters by the in situ plaque hybridization technique of Benton and Davis, *Science*, 196, 180–182 (1977). The prehybridization solution is maintained at 55° C. for several hours and has the following composition: 0.75M NaCl; 0.15M Tris/HCl, pH 8.0; 10 mM EDTA; 5×Denhardt's Solution; 0.1% sodium pyrophosphate; 0.1% SDS; 100 microgram/ml *E. coli* t-RNA. The hybridization solution has the same composition except that it is maintained overnight at 45° C., and contains labeled probe in a concentration of about 0.5×10^6 cpm/mL. After hybridization, the filters are washed four times in 1 X SSC (=0.15M NaCl, 0.015M Na_3-citrate) and exposed to x-ray film.

This screening procedure yields 50 plaques which hybridize to TB21 on both sets of filters. These 50 individual plaques are picked and combined into 10 culture pools

containing 5 plaques each. The 10 cultures are grown and DNA is isolated from 50 ml phage lysates. This DNA is then digested with EcoRI and fractionated on two identical 1% agarose gels. after which it is transferred to nitrocellulose paper according to the method of Southern, *J. Mol. Biol.*, 98, 503–4517 (1975).

The DNAs on the two filters are hybridized to ^{32}P labeled TB21 and TB36, respectively. Individual plaques from the pool containing a restriction fragment which strongly hybridizes to both probes are then screened according to the above procedure, except that the DNAs are digested with EcoRI, BamHI, and EcoRI plus BamHI. In this way the 6.8kb EcoRI-BamHI fragment containing human beta FSH is isolated.

A partial restriction map of clone 15B, containing the 6.8kb EcoRI-BamHI fragment is shown in FIG. 2. In order to locate the position of the beta FSH sequences within the 1.1 kb HindIII-KpnI and a 1.4 kb PstI fragment. Partial DNA sequencing of these two fragments shows that this DNA indeed codes for human beta FSH and that the entire coding region for beta FSH is contained in these two fragments.

As shown by the restriction map of FIGS. 3-3A, the beta FSH coding sequence is interrupted by an intervening sequence of approximately 1.6 kb between amino acids 35 and 36 of mature beta FSH. The nucleotide sequence of the entire human beta FSH coding region and some of the flanking and intervening sequences are given below. The amino acid sequence deduced from the nucleotide sequence is given for the coding region.

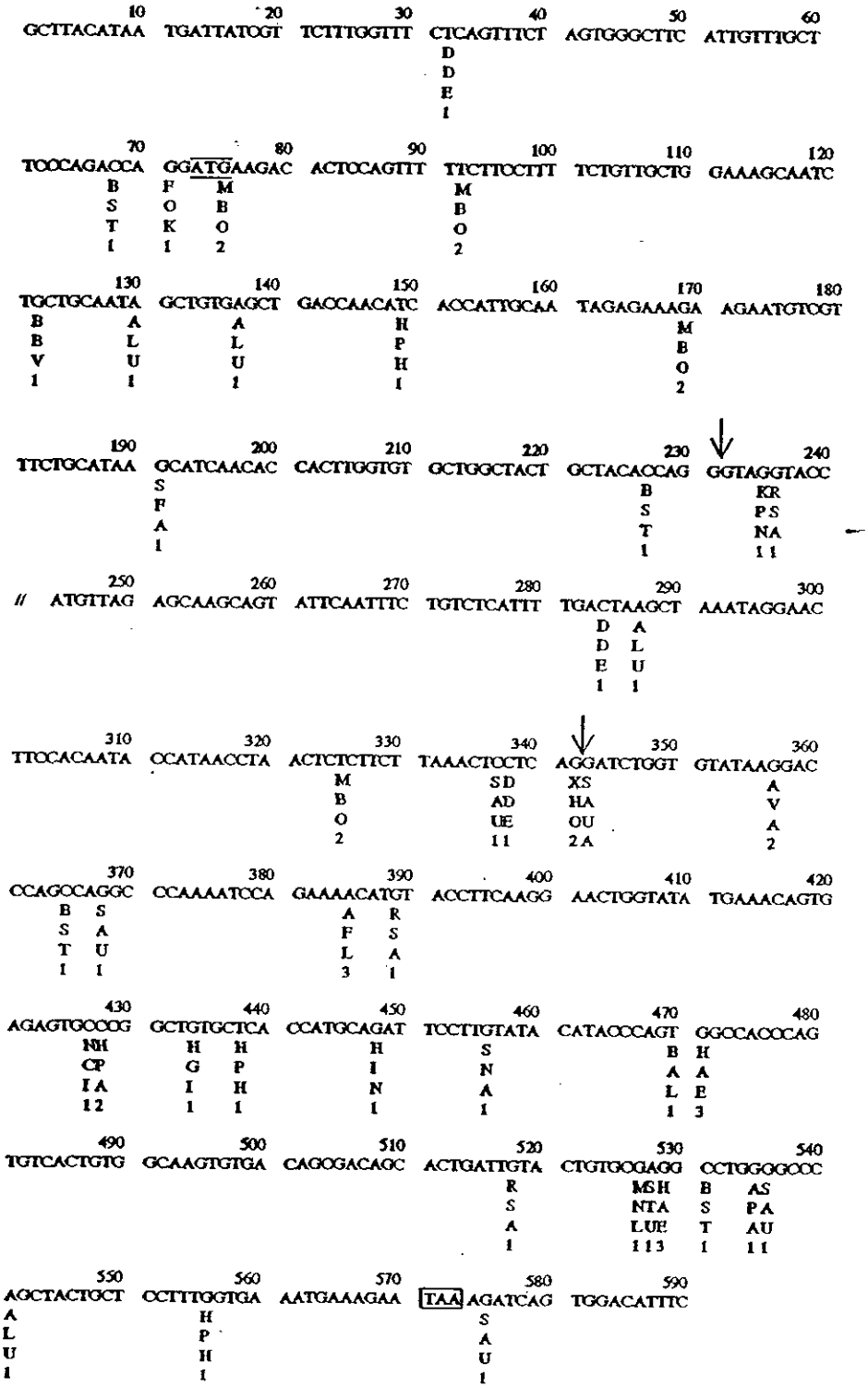
```
                                                30                                                  60
GCT TAC ATA ATG ATT ATC GTT CTT TGG TTT CTC AGT TTC TAG TGG GCT TCA TTG TTT GCT

                                              .90                                                  120
TCC CAG ACC AGG [ATG] AAG ACA CTC CAG TTT TTC TTC CTT TTC TGT TGC--TGG AAA GCA ATC
                [Met] Lys Thr Leu Gln Phe Phe Phe Leu Phe Cys Cys Trp Lys Ala Ile

                                             150                                                  180
TGC TGC AAT AGC TGT GAG CTG ACC AAC ATC ACC ATT GCA ATA GAG AAA GAA GAA TGT CGT
Cys Cys Asn Ser Cys Glu Leu Thr Asn Ile Thr Ile Ala Ile Glu Lys Glu Glu Cys Arg

                                             210                                                  240
TTC TGC ATA AGC ATC AAC ACC ACT TGG TGT GCT GGC TAC TGC TAC ACC AGG↓GTA GGT ACC
Phe Cys Ile Ser Ile Asn Thr Thr Trp Cys Ala Gly Tyr Cys Tyr Thr Arg

//  ATG TTA GAG CAA GCA GTA TTC AAT TTC TGT CTC ATT TTG ACT AAG CTA AAT AGG AAC
                                             270                                                  300

                                             330                                                  360
TTC CAC AAT ACC ATA ACC TAA CTC TCT TCT TAA ACT CCT CAG↓GAT CTG GTG TAT AAG GAC
                                                     Asp Leu Val Tyr Lys Asp

                                             390                                                  420
CCA GCC AGG CCC AAA ATC CAG AAA ACA TGT ACC TTC AAG GAA CTG GTA TAT GAA ACA GTG
Pro Ala Arg Pro Lys Ile Gln Lys Thr Cys Thr Phe Lys Glu Leu Val Tyr Glu Thr Val

                                             450                                                  480
AGA GTG CCC GGC TGT GCT CAC CAT GCA GAT TCC TTG TAT ACA TAC CCA GTG GCC ACC CAG
Arg Val Pro Gly Cys Ala His His Ala Asp Ser Leu Tyr Thr Tyr Pro Val Ala Thr Gln

                                             510                                                  540
TGT CAC TGT GGC AAG TGT GAC AGC GAC AGC ACT GAT TGT ACT GTG CGA GGC CTG GGG CCC
Cys His Cys Gly Lys Cys Asp Ser Asp Ser Thr Asp Cys Thr Val Arg Gly Leu Gly Pro

                                             570
AGC TAC TGC TCC TTT GGT GAA ATG AAA GAA [TAA] AAA TCA GTG GAC ATT TC
Ser Tyr Cys Ser Phe Gly Glu Met Glu Lys [   ]
```

clone, the 6.8 kb EcoRI-BamHI fragment of clone 15B is subcloned into pBR322 to yield plasmid p15B6.8R/B (FIG. 2). p15B6.8R/B is then digested with various restriction enzymes and the products are fractionated by agarose gel electrophoresis using conventional methods. The DNA is blotted to nitrocellulose paper and hybridized to fragments of a porcine beta FSH cDNA clone labeled with ^{32}P by nick translation.

As shown in FIG. 2, the porcine beta FSH-probe hybridizes to only two fragments of the human DNA, namely a 1.1

Still referring to the above sequence, there is a box around the ATG initiation codon of the 18 amino acid signal peptide, which is cleaved post-translationally. The mature protein begins with the amino acid Asn encoded by the circled triplet AAT. The exon-intron boundaries are marked by arrows; they are flanked by the consensus sequence GT for the splice donor and AG for the splice acceptor site. There is a box around the stop codon TAA, the end of the coding region.

Below is a reproduction of the above sequence not broken into triplets, showing restriction sites; the ATG beginning and the TAA ending the coding region are boxed and the exon-intron junctions are marked by arrows.



Insertion of the Beta FSH DNA into a BPV-Based Expression Vector

Referring to FIGS. 3–3A, a synthetic BamHI linker is inserted at the DdeI site of p15B6.8R/B, which is located 42 nucleotides 5. of the ATG initiation codon. Referring to FIG. 4, p15B6.8R/B is digested with DdeI and treated with *E. coli* DNA polymerase (Klenow), after which it is ligated to synthetic BamHI linkers and digested with BamHI. The 295 bp fragment containing the first exon of FSH is isolated and cloned into the BamHI site of pBR322. The resulting plasmid pBR295Bam is digested with KpnI plus EcoRI plus AvaI and ligated to p15B6.8R/B which has been digested with KPnI plus EcoRI plus SmaI. The ligation mix is then used to transform *E. coli*, and the plasmid pBR2.8Bam containing the human beta FSH DNA sequence as a BamHI

fragment is identified from among the transformants by restriction mapping.

As shown in FIG. 4, expression plasmid CL28FSH2.8BPV is prepared according to the same method used to prepare pRF375 (FIG. 1), except that the 2.8 kb BamHI fragment of pBR2.8Bam is used in place of the alpha hCG cDNA clone. Plasmid CL28FSH2.8BPV can be used to transform mammalian host cells using conventional methods, and human beta FSH can be isolated and purified.

Transfection of Mouse Cells

To produce heterodimeric FSH using a mixed transfection, five μg of each BPV plasmid, i.e., pRF375 (alpha subunit) and CL28FSH2.8BPV (beta FSH), are mixed and added 0.5 ml of a 250 mM $CaCl_2$ solution containing 10 μg of salmon sperm DNA as carrier. This mixture is bubbled into 0.5 ml 280 mM NaCl, 50 mM Hepes and 1.5 mM sodium phosphate. The calcium phosphate precipitate is allowed to form for 30–40 minutes at room temperature. 24 hours prior to transfection, 5×10^5 cells of mouse C127 cells (available from Dr. Dean Hamer, National Cancer Institute, NIH, Bethesda, Md.) are placed in a 100 mm dish or T-75 flask. Immediately before adding the exogenous DNA, the cells are fed with fresh medium (Dulbecco's Modified Medium, 10% fetal calf serum). One ml of calcium phosphate precipitate is added to each dish (10 ml), and the cells are incubated for 6–8 hours at 37° C.

The medium is aspirated and replaced with 5 ml of 2 glycerol in phosphate buffered saline, pH 7.0 (PBS) for 2 minutes at room temperature.

The cells are washed with PBS, fed with 10 ml of medium, and incubated at 37° C. After 20–24 hours, the medium is changed and subsequent refeeding of the cells is carried out every 3–4 days. Individual clones are grown in T-25 flasks. After 7–21 days, cell clones can be transferred to larger flasks for analysis.

Deposits

The following, described above, have been deposited in the American Type Culture Collection, Rockville, Md.:

alpha beta SVVP1, ATCC VR 2077;

alpha SVHVP1, ATCC VR 2075;

beta SVVP1, ATCC VR 2075;

pRF 375 in C127 cells, ATCC CRL 8401;

pRF 398 in C127 cells, ATCC CRL 8401;

pCL28XholHBPV *E. coli*, ATCC 39475;

pRF 398 alpha t_2 in C127 cells, ATCC CL 8400.

The following, described above, has been deposited in the Agricultural Research Culture Collection (NRRL), Peoria, Ill. 61604:

CL28FSH2.8BPV in *E. coli*, NRRL B-5923.

Use

The transformed cell lines of the invention are used to produce glycosylated biologically active heterodimeric human fertility hormones. hCG and LH made according to the invention, for example, have a number of well-known medical uses associated with human fertility. Furthermore, FSH can be used, alone or in conjunction with hCG or LH, to induce ovulation or superovulation for in vitro fertilization. In addition, heterodimeric FSH, or the beta subunit alone, can be used in diagnostic tests for fertility and pituitary functions.

Human fertility hormones produced by recombinant cells have the advantage, compared to such hormones obtained from natural sources, of being free from contamination by other human proteins, in particular other fertility hormones.

Other Embodiments

Other host cells, vectors, promoters, transforming sequences, and viruses can also be employed. The host cell employed generally is dependent on the vector being used. For example, when the vector is a replicating virus or a non-replicating viral DNA, the host cells are cells capable of being infected or transfected, respectively, by those vectors; e.g., SV40-containing vectors require monkey host cells, preferably CV-1 cells. Where the cloning vector is a plasmid having procaryotic control sequences, prokaryotic host cells, e.g., *E. coli*, are used. Where the cloning vector is a plasmid having eukaryotic control sequences, appropriate eukaryotic host cells, e.g., mouse C127 cells, are used. Besides autonomously replicating vectors, suitable vectors can be used to insert the DNA into the genome of the host cell, as is well known to those skilled in the art. As is also well known in the art, the vector may also contain an amplifiable marker, such as DHFR, particularly when used to transfect a $DHFR^-$ CHO cell line.

The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying current knowledge, readily modify and/or adapt for various applications such specific embodiments without departing from the generic concept, and therefore such adaptations and modifications are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation.

We claim:

1. A recombinantly produced biologically active heterodimeric human fertility hormone selected from the group consisting of human chorionic gonadotropin, human luteinizing hormone, and human follicle stimulating hormone, free from contamination by any other proteins of human origin.

2. A recombinantly produced hormone in accordance with claim 1, wherein said hormone is human chorionic gonadotropin.

3. A recombinantly produced hormone in accordance with claim 1, wherein said hormone is human luteinizing hormone.

4. A recombinantly produced hormone in accordance with claim 1, wherein said hormone is human follicle stimulating hormone.

* * * * *

US005650390A

United States Patent [19]

Samaritani et al.

[11] Patent Number: 5,650,390

[45] Date of Patent: Jul. 22, 1997

[54] **GONADOTROPIN CONTAINING PHARMACEUTICAL COMPOSITIONS WITH SUCROSE STABILIZER**

[75] Inventors: **Fabrizio Samaritani; Patrizia Natale**, both of Rome, Italy

[73] Assignee: **Applied Research Systems ARS Holding N. V.**, Curacao, Netherlands Antilles

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[51] **Int. Cl.**[6] **A61K 31/18**

[52] **U.S. Cl.** **514/8**; 514/53; 514/561; 562/575; 127/29

[58] **Field of Search** 514/8, 53, 561; 127/29; 562/575

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,637,640	1/1972	Huber	260/115
3,816,617	6/1974	Banik	424/100
5,128,453	7/1992	Arpaia et al.	530/398

FOREIGN PATENT DOCUMENTS

0388223	9/1990	European Pat. Off.	A61K 3/38
0448146	9/1991	European Pat. Off.	A61K 47/12
3520228	6/1984	Germany	A61K 37/36
59-109862	6/1984	Japan .	
8501959	5/1985	WIPO	C12P 21/00
8810270	12/1988	WIPO .	
8909610	10/1989	WIPO	A61K 37/02
8910407	11/1989	WIPO	C12N 15/00

OTHER PUBLICATIONS

Section Ch., Week 9025, Derwent Publications Ltd., London, GB; Class B04, AN 90-188387 & JP, A, 2 121 933 (Kagaku Shiryo Kenky) 9 May 1990 (abstract).

Section Ch., Week 8036, Derwent Publications Ltd., London, GB; Class B04, AN 80-623660 & DD, A 141 996 (Wolf I) 5 Jun. 1980 (abstract).

Primary Examiner—Gary Geist
Assistant Examiner—Rosalynd Williams

[57] **ABSTRACT**

Pharmaceutical compositions containing FSH, LH or hCG stabilized by means of a combination of sucrose and glycine. The formulation is particularly suitable for stabilizing a lyophilisate of recombinant gonadotropins.

16 Claims, No Drawings

GONADOTROPIN CONTAINING PHARMACEUTICAL COMPOSITIONS WITH SUCROSE STABILIZER

This application is a 371 of PCT/It92/00165, filed Dec. 17, 1992.

FIELD OF THE INVENTION

The present invention concerns gonadotropin containing pharmaceutical compositions. More precisely, it concerns compositions of sucrose-stabilized gonadotropins. The gonadotropins of the present invention comprise FSH (Follicle Stimulating Hormone), LH (Luteinizing Hormone) and hCG (Human Chorionic Gonadotropin).

BACKGROUND OF THE INVENTION

It is known that highly purified proteins are time-unstable and are stabilized, for instance, in admixture with saccharides, such as lactose and mannitol, or else with proteins and aminoacids, such as albumin and glycine. Other high-molecular-weight compounds, having a biological origin, as, for instance, the marine colloids, dextran and other polysaccharides and the phospholipids often work equally well. Anyway, since the gonadotropins of the present invention are administered parenterally, these excipients are not suited for an injectable composition because of their allergenicity or their insufficient solubility, in some cases because of their potential toxicity or a concourse of these effects.

The composition of lyophilised proteins is described in M. J. Pikal, BioPharm, October 1990, 25–30. There are reported examples of proteins, such as growth hormone and ribonuclease A, formulated by using stabilizing excipients such as mannitol, glycin, arginine and lactose.

In particular, the lyophilisation is described of proteins in the presence of various substances in their amorphous state, as sugars, which increase the collapse temperature and possible to obtain shorter lyophilisation times. However, it is not feasible, according to the author, to foresee a standard formulation for all the proteins, and the choice of the best formulation requires a remarkable selection work.

German patent DE 3520228 describes bioactive proteins such as lymphokines, interferons, TNF (Tumor Necrosis Factor), insulin, growth hormone, in formulations which are stabilized by means of polysaccharides comprising repetitive maltotriose units. The use of sucrose as a stabilizing agent is known, for instance, in a formulation of lyophilized orgotein, as described in U.S. Pat. No. 3,637,640. International patent application WO 89/10407 describes the formulation with sucrose of M-CSF (Macrophage-Colony Stimulating Factor); patent application WO 89/09610 describes, instead, formulations of TNF which have been stabilized with albumin, dextran, polyethylene glycol, 80 polysorbate PVP, lactose, trialose or even sucrose.

The injectable formulations of gonadotropins are obtained by a process which includes their lyophilisation in order to obtain a dry powder. Gonadotropins are highly liable to denaturization during the lyophilisation process and it is desirable to obtain stable formulations able to maintain a longer cycle life when they are stored at room temperature.

European Patent EP 448146 describes lyophilised gonadotropin containing preparations, which are stabilized by means of a dicarboxylic acid salt, as, for instance, citric acid, tartaric acid and aspartic acid. Gonadotropins which are found on the market are stabilized by means of saccharides, for instance hCG is stabilized by means of mannitol (Profasi®, SERONO) and FSH is stabilized by means of lactose (Metrodin®, SERONO).

SUMMARY OF THE INVENTION

We have now found that sucrose confers a better stability to the formulation of gonadotropins and in particular to the form of these glycoproteins which have been prepared by recombinant DNA technique.

The main object of the present invention is to provide a pharmaceutical composition comprising a solid intimate mixture of a gonadotropin, such as FSH, LH or hCG, and a stabilizing amount of sucrose, alone or in combination with other stabilizing agents.

A further object is to provide a process for the preparation of said pharmaceutical composition, the step of lyophilising an aqueous solution of the components. Another object is to provide a dosage form of said pharmaceutical composition comprising the said solid mixture hermetically closed in a sterile condition within a container suitable for storage before use and suitable for reconstitution of the mixture for injectable substances.

DETAILED DESCRIPTION OF THE INVENTION

Another object is to provide a solution for said solid mixture reconstituted into an injectable solution. In order to evaluate the excipient's effect on the stability of the active ingredients, various formulations of recombinant FSH containing 150 I.U. pro vial have been prepared with various excipients: lactose, sucrose, glycine, sucrose plus glycine, lactose plus albumin and lactose plus glycine. All the formulations have been prepared by dissolving the excipients in phosphate buffer at pH 7, except the formulation with lactose (10 mg) which has been dissolved into H_2O for injection and adjusted at pH 6.4.

The samples have been stored at 45° C. and tested with a biological assay at fixed intervals of time. Tables 1 and 2 give the results of the tests effected on two different hatches of recombinant FSH in the presence of different excipients, after 2 and 4 weeks for batch 1 (Tab. 1) and after 1 and 3 weeks for batch 2 (Tab. 2).

The biological tests have been performed in compliance with the regulations of the European Pharmacopoeia and effected in duplicate. The tests for FSH and LH are reported in the "Menotropin" monography, whereas the test for hCG is reported in the "Chorionic Gonadotropin" monography.

The results show that the most stable formulations among those tested are those containing sucrose, i.e. formulations with sucrose alone and with sucrose plus glycine. Sucrose shows, surprisingly, to be an efficient stabilizing agent against the denaturization of the gonadotropins.

The stabilizing agents which are employed in the compositions of the present invention include, therefore, sucrose alone or in combination with other excipients, preferably

aminoacids such as glycine. In particular, the stability has been studied of recombinant FSH and recombinant LH.

The gonadotropins produced according to the technique of recombinant DNA must be subjected to a high purification process in order to avoid contamination agents having a non-human origin and this high purity renders them less stable than the corresponding urinary gonadotropins.

The recombinant gonadotropins of the present invention have been prepared by expression in CHO (Chinese Hamster Ovary) cells, transformed with the corresponding recombinant DNA, according to the

TABLE 1

Batch 1 of recombinant FSH I.U.

Excipient	Amount (mg)	Theoretical titer	T = 0	45° C. 2 weeks	45° C. 4 weeks
Lactose	10	167.31	129.0	139.0	104.0
Lactose	30	167.31	132.0	118.0	116.0
Sucrose	30	167.31	158.0	163.0	136.0
Sucrose	50	167.31	140.0	135.0	150.0*
Sucrose + Glycine	20 + 10	167.31	144.0	143.0	186.0
Lactose + Albumin	20 + 3	167.31	127.0*	134.0	128.0
Glycine	20	167.31	132.0	107.0	—
Lactose + Glycine	20 + 10	167.31	153.0	132.0	104.0

*valid only one assay

TABLE 2

Batch 2 of recombinant FSH 150 I.U.

Excipient	Amount (mg)	Theoretical titer	T = 0	45° C. 1 week	45° C. 4 weeks
Lactose	10	155.08	163.0	121.0	103.0
Lactose	30	155.08	164.0	166.0	108.0
Sucrose	30	155.08	165.0	128.0	151.0
Sucrose	50	155.08	150.0	143.0	157.0
Sucrose + Glycine	20 + 10	155.08	160.0	152.0	185.0
Lactose + Glycine	20 + 3	155.08	172.0	136.0	101.0
Glycine	20	155.08	136.0	115.0*	97.0*
Lactose + Albumin	20 + 10	155.08	171.0*	137.0	157.0

*valid only one assay

techniqué described in European patents EP 160699 and EP 211894.

The close study of recombinant-FSH-containing formulations has been performed by using different compositions, according to the lay-out of Tab. 3, respectively comprising: a) lactose, b) sucrose, c) sucrose plus glycine.

The lyophilisate was prepared by diluting the bulk of gonadotropin with a solution of the excipient in water for injection ("a" formulation) or 0.01M phosphate buffer ("b" and "c" formulations) in order to achieve the concentration of 200 I.U./ml, adjusting the pH at 6.4 for the lactose-containing formulations and at 7 for the sucrose containing or sucrose-plus-glycin-containing formulations. The solution has been filtered, brought to the final volume with the remaining solution of the excipient in order to achieve the concentration of 150 I.U./ml and lyophilized.

The accelerated stability of these formulations has been studied so that the stability of the same can be foreseen when they are stored in containers at room temperature, through the extrapolation of the data obtained at higher temperatures (+37° C.; +45° C.; +50° C.).

The accelerated stability of the FSH formulations has been determined through the biological activity test, performed at the time intervals which are reported in the corresponding Tables.

Two ampoule preparations of HMG (Menotropin) were used as standard solutions, the first having a biopotency of 101.3 I.U. FSH/ampoule and 85.6 I.U. LH/ampoule, the second having a biopotency of 103.1 I.U. FSH/ampoule and 82.3 I.U. LH/ampoule. The samples, at

TABLE 3

Formulations of recombinant FSH

Composition	Dosimetry I.U.	Lactose mg	Sucrose mg	Glycine mg	$Na_2HPO_4.7H_2O$ mg	$NaH_2PO_4.H_2O$ mg
a	150	10	—	—	—	—
b	150	—	30	—	1.11	0.45
c	150	—	20	10	1.11	0.45

the concentrations 0.5; 1.0 and 2.0 I.U./ml, as well as the standard HMG solutions, were administered to three different groups of five rats each, through subcutaneous injection of 0.5 ml/rat twice a day for three consecutive days (final doses: 1.5; 3.0; 6.0 I.U. FSH/rat). Each animal further received altogether a dose of 40 I.U. hCG.

Data reported in Tab. 4 refer to formulations of 3 different batches of recombinant FSH, containing 150 I.U./ml FSH, in the presence of 10 mg lactose (Composition a), 30 mg sucrose (Composition b) and 20 mg sucrose plus 10 mg glycine (Composition c) in 5 ml vials. The tests were performed at the temperatures 37° C. 45° C. and 50° C.

The degradation was significant for the lactose containing formulations for all the test temperatures and for all the three batches. On the contrary, no appreciable variation was observed for the sucrose containing formulation of batch 1 at the same temperatures. For the formulation containing sucrose plus glycine relating to the first batch, the only appreciable degradation was observed at 50° C. For the formulations with sucrose or sucrose+glycine of the remaining batches, a degradation is observed which was lower anyway than that of the lactose containing formulation.

Tab. 5 gives further accelerated stability data, derived by the biological activity data, for 2 different batches (batch 1 and batch 2) of recombinant FSH formulations containing 150 I.U./ml FSH and 30 mg sucrose in 3 ml vials.

The study was performed on vials stored for 5 weeks at the temperature of 50° C. or for 10 weeks at the

TABLE 4

Study of the accelerated stability of recombinant FSH formulation (3 different batches - Batch 1, Batch 2 and Batch 3 containing 150 LU/ml FSH) with lactose 10 mg (Composition a), sucrose 90 mg (Composition b) and sucrose (20 mg) + glycine (10 mg) (Composition c) in 5 ml vials.

Batch 1

	50° C.				45° C.					37° C.			
	T = 0	1 W	3 W	5 W	2 W	4 W	8 W	10 W	11 W	3 W	5 W	9 W	12 W
a	147	126	124*	83	163*	84	105	109	—	140*	109	97	122*
b	156	154	155	151	154	119	115	—	164	165	165	168	151
c	160	179	143	114	160	134	133	148	—	136	156*	132	175

Batch 2

	50° C.				45° C.				37° C.			
	T = 0	1 W	2 W	5 W	2 W	6 W	8 W	10 W	5 W	7 W	10 W	12 W
a	135	50*	40*	—	96*	51	43	—	134	108	104	90
b	112	152*	134	96	125	94	89	101	157	163	135	114*
c	145	173*	124	118	143	145	154	135	146	154	139	141

Batch 3

	50° C.				45° C.				37° C.			
	T = 0	1 W	3 W	5 W	2 W	4 W	8 W	10 W	3 W	5 W	9 W	12 W
a	144	40*	30*	—	135	80*	20*	—	106	70	34	—
b	152	136	138	110	161	136	106	110	165	179	159	140
c	135	140	176	125	163	142	122	125	151	151	158	176

W = weeks
* = only one assay valid

TABLE 5

Study of the accelerated Stability of recombinant FSH formulations (105 I.U.) with sucrose (30 mg) in 3 ml vials

	50° C.					45° C.				37° C.			
	T = 0	1 W	2 W	3 W	5 W	2 W	4 W	8 W	10 W	3 W	5 W	9 W	12 W
Batch 1	141	135	113	136	140	*135	*149	179	166	147	145	149	122
Batch 2	152	144	126	132	*146	135	167	160	162*	154	146	152	175

W = Weeks
*only one assay valid

temperature of 45° C. or for 12 weeks at the temperature of 37° C. Again, no activity variation was observed at all the test temperatures for both batches.

The stability forecast at room temperature, given in Tab. 6 and extrapolated from the accelerated stability data of Tab. 5 according to the Garret's method (Garret E. R., J. Pharm. Sci., 51:811, 1962) shows a degradation of about 35% and 80% after two years of storage at 4° C. and 25° C. respectively for the lactose containing formulations.

No degradation is foreseen at 4° C. for the formulations with sucrose or sucrose plus glycine, whereas only a 6% decrease is foreseen for the sucrose containing formulations after two years at 25° C.

The stability has been studied of recombinant LH formulations (75 I.U.) with 50 mg sucrose (Composition a) and 50 mg lactose (Composition b). The exact composition of recombinant LH formulations is given in Table 7.

The study of the accelerated stability of such formulations stored at 37° C., 45° C. and 50° C., determined through the biological activity test measured in I.U. (Table 8) shows what has been already observed for the FSH formulations: the degradation of the sucrose containing preparations was extremely low, whereas the degradation of the lactose containing formulations was more evident.

The stability forecast at room temperature stability extrapolated from the accelerated stability data of Table 8 according to the Garret's method (Garret E. R., J. Pharm. Sci., 51:811, 1962) is given in Table 9.

A degradation is calculated of about 20% and 8% respectively for the lactose formulations stored for two

TABLE 6

Stability forecast of recombinant FSH formulations (150 I.U.) at room temperature

Composition	Excipient	Activity recovery (%) 4° C. 1 year	4° C. 2 years	25° C. 1 year	25° C. 2 years
a	Lactose	79.30%	62.89%	41.57%	17.28%
b	Sucrose	99.61%	99.22%	96.86%	93.82%
c	Sucrose + Glycine	no degradation		no degradation	

TABLE 7

Composition of recombinant LH formulations (75 I.U.) with sucrose 50 mg (Composition a) and lactose 50 mg (Composition b) in 3 ml vials

Composition	Excipient	Amount (mg)
a	Sucrose	47.75
	$NaH_2PO_4.H_2O$	0.052
	$Na_2HPO_4.2H_2O$	0.825
b	Lactose	50.00
	$NaH_2PO_4.H_2O$	0.052
	$Na_2HPO_4.2H_2O$	0.825

TABLE 8

Study of the accelerated stability of recombinant LH formulation (75 I.U.) in 3 ml vials

Excipient	50° C. T = 0	1 W	2 W	5 W
mg				
Sucrose 47.75	71 (58–86)	67* (34–121)	55 (42–73)	59 (47–76)
Lactose 50	77 (64–93)	57* (37–81)	34* (15–56)	40 (32–50)

Excipient	45° C. 2 W	5 W	8 W	12 W	37° C. 6 W	9 W	12 W
mg							
Sucrose 47,75	65 (50–85)	—	59 (47–73)	57 (44–75)	67* (51–86)	70* (51–96)	72 (55–94)
Lactose 50	39 (29–52)	50* (33–79)	36* (20–57)	—	44* (32–60)	42* (31–56)	48 (38–62)

*Only one assay valid
(In brackets the confidential limits)
W = weeks

TABLE 9

Stability forecast of recombinant LH formulations (75 I.U.) at room temperature

Compositions	Excipient	Activity recovery % 4° C.	after 2 years 25° C.
a	Sucrose	99.68%	90.65%
b	Lactose	80.56%	19.86%

years at 4° C. and 25° C. The sucrose containing formulations remain unchanged for two years at 4° C. and a decrease of only 9% is calculated for the same formulations after two years at 25° C.

A study was also performed on urinary hCG formulations by using sucrose (formulation "a", 30 mg sucrose), lactose (formulation "b", 10 mg lactose) or mannitol (formulation "c", 20 mg mannitol) as stabilizers in 3 ml vials containing 500 I.U./vial hCG.

Tab. 10 gives the estimated values derived by the biological assay performed at different times for said hCG formulations stored at a temperature of 55° C.

Once again, sucrose is shown to be the most suited excipient in order to preserve hCG stability, i.e. an excipient which is much better than mannitol and better than lactose, even if, in this case, the stability difference for the three formulations is less strong with respect to the FSH or LH case.

EXAMPLES OF PHARMACEUTICAL MANUFACTURING

Materials: extra pure sucrose Ph Eur, BP, PH Nord, NF (Merck); lactose RPE ACS (Carlo Erba); glycine for analysis use (Merck), $NA_2HPO_4.2H_2O$ for analysis use (Merck), $NaH_2PO_4.H_2O$ RPE (Carlo Erba); 85% phosphoric acid RPE ACS (Carlo Erba); 0.1M NaOH (Merck); water for injectables.

As containers, 3 or 5 ml glass vials were used (type I borosilicate glass) with rubber fastener (Fradagrada Pettenati and Pharmagummi, butyl mixture) and aluminum ring.

Preparation of the Sucrose Containing Recombinant FSH Solution (for 1,200 Vials Containing Each 150 I.U. FSH)

Sucrose (36 g) $Na_2HPO_4.2H_2O$ (1.33 g) and $NaH_2PO_4.H_2O$ (0.54 g) were dissolved into water for injectables (1,200 ml) in order to obtain the starting sucrose solution. The bulk of recombinant FSH (180.000 I.U.) was diluted with the solution so that an FSH solution was obtained at 200 I.U./ml.

The pH of the FSH solution and of the residual sucrose solution was adjusted at 7 by means of 0.1M NaOH or H_3PO_4. The FSH containing solution was filtered through a Durapore 0.22 um sterile filter and brought to the final volume with the residual excipients solution filtered through the same Durapore filter. During the process the solution temperature was kept between 4° and 8° C.

TABLE 10

Study of stability at 55° C. of hCG formulations (500 I.U.) with sucrose (a), lactose (b) and mannitol (c)

Composition	T = 0	3 W	6 W
a	511 (390.1–670.2)	567 (407.0–788.7)	597 (452.2–789.4)
b	534 (396.7–719.6)	355 (293.7–430.2)	428 (330.2–555.01)
c	449 (330.2–611.7)	332 (259.0–425.5)	244 (201.8–295.9)

W = weeks (Between brackets confidential 95% limits)

Preparation of the Sucrose Containing Recombinant LH Solution (for 1,200 Vials Each Containing 75 I.U. LH)

Sucrose (57.3 g), $Na_2HPO_4.2H_2O$ (0.99 g) and $NaH_2PO_4.H_2O$ (0.62 g) were dissolved into water for injectables (600 ml) in order to obtain the starting sucrose

solution. The recombinant LH bulk (90,000 I.U.) was diluted with the sucrose solution so that an LH solution is obtained at 300 I.U./ml.

The pH of the LH solution and of the residual sucrose solution was adjusted at 8 by means of 0.1M NaOH or H_3PO_4. The LH containing solution was filtered through a 0.22 um Durapore sterile filter and brought to the final volume by means of the residual excipients solution filtered through the same Durapore filter. During the process the solution temperature was kept between 4° and 8° C.

The solutions containing different excipients were prepared in a similar manner.

Filling Up and Lyophilisation

3 ml or 5 ml vials were filled with 1 ml of FSH solution or 0.5 ml of LH solution, transferred to the freeze-dryer and cooled at −45° C. for 6 hrs. at least. The lyophilisation was started at the temperature of −45° C. with a 0.07 vacuum. The heating was performed according to the following scheme: +20° C. for 20 hrs., then ±35° C. until the end of the cycle.

On the reconstituted solution the usual quality controls were performed. Although the present invention has been illustrated by means of specific examples, it is understood that variations can be introduced without departing from the spirit and scope of the invention.

We claim:

1. A pharmaceutical composition comprising a solid intimate mixture of gonadotropin and a stabilizing amount of sucrose in combination with glycine.

2. A pharmaceutical composition according to claim 1 wherein the sucrose is between 20 and 50 mg per unit dosage.

3. A pharmaceutical composition according to claim 1, wherein the solid intimate mixture is a lyophilisate.

4. A pharmaceutical composition according to claim 3, wherein the gonadotropin is FSH, or LH or hCG.

5. A pharmaceutical composition according to claim 1, wherein the gonadotropin is recombinant.

6. A pharmaceutical composition according to claim 1, containing 75 or 150 I.U. of FSH, 30 mg of sucrose, and an effective amount of glycine.

7. A pharmaceutical composition according to claim 1, containing 75 or 150 I.U. of LH, 47.75 mg of sucrose, and an effective amount of glycine.

8. A pharmaceutical composition according to claim 4, wherein the gonadotropin is recombinant.

9. A process for preparing a pharmaceutical composition according to claim 1 comprising preparing an aqueous solution of the components, distributing the components within containers, and drying or lyophilizing the solution within the containers.

10. A process according to claim 9, wherein the pH of the solution is within the range 6.5–8.5.

11. A process according to claim 10, wherein the pH of the solution is 7 for the FSH formulation and 8 for the LH formulation.

12. Forms of presentation of said pharmaceutical composition consisting essentially of the solid mixture according to claim 1, hermetically closed in a sterile condition in a container suited for storage before use and reconstitution of the mixture in a solvent or a solution for injectables.

13. A solution comprising the solid mixture according to claim 12, reconstituted in a solvent or a solution for injectables.

14. Forms of presentation of said pharmaceutical composition comprising the solid mixture according to claim 8, hermetically closed in a sterile condition in a container suited for storage before use and reconstitution of the mixture in a solvent or a solution for injectables.

15. Forms of presentation of said pharmaceutical composition comprising the solid mixture according to claim 1, hermetically closed in a sterile condition in a container suited for storage before use and reconstitution of the mixture in a solvent or a solution for injectables.

16. Forms of presentation of said pharmaceutical composition comprising the solid mixture according to claim 1, hermetically closed in a sterile condition in a container suited for storage before use and reconstitution of the mixture in a solvent or a solution for injectables, wherein the gonadotropin is FSH, LH or hCG.

* * * * *

14. PATENT CERTIFICATION

Pursuant to Title 21 of the United States Code Section 355(b)(1), Serono, Inc. has reviewed the records of the U.S. Patent and Trademark Office and is of the opinion that there are no United States patents to which Serono, Inc. does not have a license which claim recombinant human luteinizing hormone (r-hLH) or a method of using r-hLH with respect to which a claim of patent infringement could reasonably be asserted against Serono, Inc. in connection with the manufacture, use and sale of r-hLH for the treatment of female infertility.

Pamela Williamson Joyce
Vice President, Regulatory Affairs

April 10, 2001
Date

20. OTHER

20.1 MARKETING EXCLUSIVITY

On October 7, 1994, Luveris™ was granted orphan-drug designation (application number ( )) for the indication that is the subject of this NDA.

Upon approval of this NDA, Serono, Inc. intends to claim market exclusivity pursuant to 21 CFR 316.31(a).

A copy of the letter from the Office of Orphan Products Development is provided on the following pages.

20.2 WAIVER OF REQUIREMENT FOR CONDUCTING PEDIATRIC STUDIES

In accordance with 21 CFR 314.55 (c)(2), Serono respectfully requests a full waiver of the requirement for conducting pediatric studies with Luveris™. Since Luveris™ is indicated for the treatment of infertile women, its administration in the pediatric population is not warranted.

In accordance with 21 CFR 314.55(c)(2), the undersigned hereby certifies the following:

The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients;

Not applicable

Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed; or

Not applicable

There is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups.

Not applicable

Pamela Williamson Joyce
Vice President Regulatory Affairs

Date

EXCLUSIVITY SUMMARY FOR NDA # 21-322 SUPPL #_____

Trade Name Luveris® Generic Name lutropin alfa for injection

Applicant Name Serono, Inc. HFD 580

Approval Date If Known October 8, 2004

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_X_/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505 (b) (1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

7 years (orphan indication)

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /__X_/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /__X_/ NO /__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 17-646 Pergonal

NDA# 21-047 Repronex

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to

question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 6253, Study 21008

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 21008 Study 6253

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # 44,108 YES /_X__/ ! NO /___/ Explain: _____

Investigation #2 !

IND # 44,108 YES /_X__/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

Signature Archana Reddy, M.P.H. Date: October 7, 2004
Title: Regulatory Project Manager

Signature of Office/ Division Director Daniel Shames, M.D. Date October 8, 2004

Form OGD-011347 Revised 05/10/2004

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

/s/

Daniel A. Shames
10/8/04 02:08:29 PM

NDA 21-322
Luveris (lutropin alfa for injection) 75 I.U.
Serono, Inc.

Exclusivity Summary

This application is not being approved. An exclusivity summary is not necessary.

AR
2/07/02

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-322 **Supplement Type (e.g. SE5):** N/A **Supplement Number:**

Stamp Date: May 26, 2004 **Action Date:** November 26, 2004

HFD-580 **Trade and generic names/dosage form:** Luveris® (lutropin alfa for injection)

Applicant: Serono, Inc. **Therapeutic Class:** 3s

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Stimulation of follicular development in infertile hypogonadotropic hypogonadal women with profound LH deficiency (LH < 1.2 IU/L).

Is there a full waiver for this indication (check one)?

☒ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply:** ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

X **Products in this class for this indication have been studied/labeled for pediatric population**
☒ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: **NDA 21-322**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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/s/

Archana Reddy
10/6/04 12:36:53 PM

NDA 21-322
Luveris (lutropin alfa for injection) 75 I.U.
Serono, Inc.

Pediatric Page

No pediatric page is required if NA action.

CM
2/6/02

16. DEBARMENT CERTIFICATION

Debarment Certification Statement

In accordance with Section 306(k)(1) of the Federal Food, Drug, and Cosmetic Act, the undersigned hereby certifies that Serono, Inc. did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306 (a) or (b)], in connection with this application.

Rosann J. Reinhart

Rosann J. Reinhart
Executive Director, Regulatory Affairs

25-JAN-2001
Date

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: June 8, 2001

From: Jeanine Best, M.S.N., R.N.
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: NDA 21-322

I have reviewed the financial disclosure information submitted by Serono, Inc. in support of their NDA 21-322, Luveris™ (lutropin alfa for injection).

Five studies were conducted to assess the safety and efficacy of Luveris™. This product is proposed for concomitant administration with r-hFSH for the induction of ovulation in infertile women with severe LH [ ] deficiency. The study numbers and the results of the review of financial disclosure documents are summarized below:

Study Number/Title	Study Status	Financial Disclosure Review
Study 6253 / "An Open Label, Randomized, Dose-Finding, Multicenter, Pivotal Study to Determine the Minimal Effective Dose and To Assess the Safety of Recombinant Human Leutinizing Hormone (r-hLH) to Support Recombinant Human Follicle Stimulating Hormone (r-hFSH) induced Follicular Development in LH and FSH Deficient Anovulatory Women (WHO Group I)"	Completed prior to 2/2/99	Appropriate documentation received, no financial disclosure submitted.
Study 21008/ "A Phase II, Prospective, Randomized, Controlled, Double-Blind, Multicenter Study to Confirm the Efficacy and Safety of Recombinant Human Leutinizing Hormone (r-hLH), 75 IU, Administered Subcutaneously, to support recombinant Human Follicle Stimulating Hormone (r-hFSH)-Induced Follicular development in Women with Hypogonadotropic Hypogonadism and Severe LH Deficiency who Desire Pregnancy"	Ongoing after 2/2/99	Appropriate documentation received, no financial disclosure submitted.

Study 6905/ " An Open, Randomized, Dose Finding, Multicenter, Study to Determine the Minimal Effective Dose and to Assess the Safety of r-hLH to support r-hFSH induced Follicular Development in Anovulatory Women with Hypogonadotropic Hypogonadism"	Completed prior to 2/2/99	Appropriate documentation received, no financial disclosure submitted.
Study 7798/ "A Phase III Multicenter Study for the Evaluation of the Efficacy and Safety of Recombinant Human Leutinizing Hormone (f-hLH) to support Recombinant Human Follicle Stimulating Hormone (r0hFSH)-Induced Follicular development in LH and FSH deficient Anovulatory Women (WHO Group I)"	Completed prior to 2/2/99	
Study 8297/ "A Phase III Multicenter, Non-Comparative Study to Evaluate the Efficacy and Safety of Recombinant Human Leutinizing Hormone (r-hLH) to support Human Follicle Stimulating Hormone (r-FSH)-Induced Follicular Development in LH and FSH Deficient Anovulatory Women (WHO Group I)"	Completed prior to 2/2/99	

Documents Reviewed:

- Financial Certification Information submitted April 30, 2001.

Study 6253

This study was completed prior to February 2, 1999. There were 16 principal and subinvestigators (investigators) at 10 sites in this trial.

- Site #8 had 1 principal investigator (only investigator at this site) for whom financial disclosure information was not received; the sponsor was notified of his death upon retrospectively requesting the completion of the financial disclosure form; this site enrolled 5.3% of the patients in the study
- Site #4 had 1 subinvestigator for whom financial disclosure information was not received; this subinvestigator has retired and the sponsor is unable to locate; this site enrolled 13.2% of the patients in the study

Of the remaining investigators, none had any disclosable information.

Study 21008

There were 44 principal and subinvestigators (investigators) at 25 sites in this trial. Financial disclosure information was received for all investigators; none had any disclosable information.

Study 6905
There were 51 principal and subinvestigators (investigators) at 14 sites in this trial.

- Site #1 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 4.7% of the patients
- Site #4 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 9.3% of the patients

Of the remaining investigators, none had any disclosable information.

Study 7798
There were 14 principal and subinvestigators (investigators) at 10 sites in this trial. Financial disclosure information was received for all investigators; none had any disclosable information.

Study 8297
There were 30 principal and subinvestigators (investigators) at 14 sites in this trial. Financial disclosure information was received for all investigators; none had any disclosable information.

Conclusion:
Adequate documentation was submitted to comply with 21 CFR 54. The sponsor performed due diligence in collecting financial disclosure information from investigators for all studies, even those completed prior to February 2, 1999, and the rate of return was acceptable for all studies. There was no disclosure of financial interests that could bias the outcome of the trials.

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

/s/

Jeanine Best
6/8/01 01:44:39 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	see attached list of Clinical Investigators	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Pamela Williamson Joyce	Vice President, US Regulatory Affairs
FIRM/ORGANIZATION: Serono, Inc.	
SIGNATURE: Pamela W. Joyce	DATE: February 27, 2001

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

19. FINANCIAL DISCLOSURE

19.1. FINANCIAL DISCLOSURE OBTAINED FROM THE FOLLOWING INVESTIGATORS AND SUBINVESTIGATORS

Investigator Name/Address	Protocol No.	Type of Study	Center No.	No. of Patients Entered	Subinvestigators
Bowman, Mark Sydney IVF Level 11 4 O'Connell Street Sydney NSW Australia	21008	Ph. III	417	1	None
Chantilis, Samuel 8160 Walnut Hill Lane Suite 320 Dallas, TX 75231	21008	Ph. III	258	1	
Coutifaris, Christos University of Pennsylvania Department of Obstetrics and Gynecology 106 Dulles Building 3400 Spruce Street Philadelphia, PA 19104	21008	Ph. III	48	1	
DeVane, Gary Center for Infertility and Reproductive Medicine 3435 Pinehurst Avenue Orlando, FL 32804-4002	21008	Ph. III	128	1	
Dunaway, Heber Fertility & Laser Center 4720 I-10 Service Road Suite 100 Metairie, LA 70001	21008	Ph. III	282	1	
Dunn, Randall Obsterical and Gynecological Associates, P.A. 7550 Fannin Street Houston, TX 77054	21008	Ph. III	127	2	
Elsner, Carlene Southeastern Fertility Institute 5505 Peachtree Dunwoody Road Suite 400 Atlanta, GA 30342	21008	Ph. III	264	1	

Investigator Name/Address	Protocol No.	Type of Study	Center No.	No. of Patients Entered	Subinvestigators
Feigenbaum, Seth Kaiser Permanente Medical Center Department of Obstetrics and Gynecology 7 Southwest 2238 Geary Street San Francisco, CA 94115-3394	21008	Ph. III	259	1	[redacted]
Gill, Inderbir F.I.R.S.T. IVF 5400 Mackinaw Street Suite 2400 Saginaw, MI 48604	21008	Ph. III	283	1	None
Gutmann, Jacqueline Women's Institute 815 Locust Street Philadelphia, PA 19107	21008	Ph. III	439	1	None
Haas, Gilbert Center for Reproductive Health, P.C. 1000 N. Lincoln Suite 300 Oklahoma City, OK 73104	21008	Ph. III	415	1	None
Hughes, Graeme Prince of Wales Private Hospital Suite 12, Level 7 Barker Street Randwick NSW 2031 Australia	21008	Ph. III	438	2	[redacted]
Hull, Magdalen Winthrop University Hospital 259 First Street Mineola, NY 11501	21008	Ph. III	251	1	None
Kaplan, Paul Women's Care Fertility Center 590 Country Club Road Suite A Eugene, OR 97401	21008	Ph. III	434	1	[redacted]
Kaufman, Robert Southeastern Fertility Center, P.A. 1375 Hospital Drive Mt. Pleasant, SC 29464	21008	Ph. III	252	2	[redacted]
Moffitt, Drew Arizona Reproductive Medicine Specialists 1300 North 12th Street Suite 520 Phoenix, AZ 85006	21008	Ph. III	284	1	[redacted]

Investigator Name/Address	Protocol No.	Type of Study	Center No.	No. of Patients Entered	Subinvestigators
Neal, Gregory Fertility Center of San Antonio 4499 Medical Drive Suite 360 San Antonio, TX 78229	21008	Ph. III	436	1	None
Odem, Randall Department of Obstetrics and Gynecology Washington University School of Medicine 4444 Forest Park Avenue Suite 3100 St. Louis, MO 63108	21008	Ph. III	94	1	[ ]
Olantunbosun, Femi Royal University Hospital 103 Hospital Drive Saskatoon, SK S7N 0W8 Canada	21008	Ph. III	432	1	[ ]
Shoham, Zeev Kaplan Hospital Department of Obstetrics and Gynecology 76100 Rehovot, Israel	21008	Ph. III	392	4	None
Smith, Howard Westmead Fertility Centre Westmead Hospital Westmead NSW 2145 Australia	21008	Ph. III	418	4	[ ]
Soto-Albors, Carlos Northern California Fertility Medical Center 4065 Sunrise Avenue Suite 310 Roseville, CA 95661	21008	Ph. III	109	1	[ ]
Stadtmauer, Laurel North Carolina Center for Reproductive Medicine 400 Asheville Ave. Suite 200 Cary, NC 27511	21008	Ph. III	262	3	None
Vaughn, Thomas Texas Fertility Center 3705 Medical Parkway Suite 420 Austin, TX 78705	21008	Ph. III	254	2	[ ]

Investigator Name/Address	Protocol No.	Type of Study	Center No.	No. of Patients Entered	Subinvestigators
Yeko, Timothy USF College of Medicine Department of Obstetrics and Gynecology Harbour Side Medical Tower 4 Columbia Drive, Suite 529 Tampa, FL 33606	21008	Ph. III	253	3	[redacted]
Baird, D. University of Edinburgh Edinburgh, UK	6253	Ph. II/III	6	6	None
Bouchard, Philippe Hospital Saint Antoine Paris, France	6253	Ph. II/III	1	2	[redacted]
Cittadini, E. Universita degli Studi de Palermo Palermo, Italy	6253	Ph. II/III	9	6	None
Flamigni, Carlo Universita degli Studi de Bologna Bologna, Italy	6253	Ph. II/III	10	4	[redacted]
Franks, S. St. Mary's Hospital London, UK	6253	Ph. II/III	5	2	[redacted]
Homburg, Roy Hasharon Hospital Petah Tikva, Israel	6253	Ph. II/III	3	6	None
Jacobs, H. The Middlesex Hospital London, UK	6253	Ph. II/III	7	1	None
Schaison, G. Hopital Kremlin Bicetre Kremlin Bicetre, France	6253	Ph. II/III	2	4	[redacted]
Shoham, Zeev Kaplan Hospital Rehovot, Israel	6253	Ph. II/III	4	5	[redacted]
Berga, Sara Department of Obstetrics and Gynecology Magee Women's Hospital Forbes Avenue and Halket St Pittsburgh, PA 15213	6905	Ph. II/III	1	2	[redacted]
DeVane, Gary Center for Infertility and Reproductive Medicine 3435 Pinehurst Avenue Orlando, FL 32804	6905	Ph. II/III	10	5	[redacted]

Investigator Name/Address	Protocol No.	Type of Study	Center No.	No. of Patients Entered	Subinvestigators
Feigenbaum, Seth Kaiser Permanente Medical Center OB/GYN Annex 2200 O'Farrell Street San Francisco, CA 94115	6905	Ph. II/III	16	6	[redacted]
Hansen, Keith Department of Obstetrics and Gynecology The Medical College of Georgia 1120 15th Street CJ-134 Augusta, GA 30912	6905	Ph. II/III	12	4	[redacted]
Martin, Kathryn Massachusetts General Hospital Reproductive Endocrine Unit Fruit Street Boston, MA 02114	6905	Ph. II/III	3	4	[redacted]
Massey, Joseph Southeastern Fertility Institute 5505 Peachtree Dunwoody Road Atlanta, GA 30342	6905	Ph. II/III	15	2	[redacted]
Odem, Randall Washington University School of Medicine 4911 Barnes Hospital Plaza St. Louis, MO 63110	6905	Ph. II/III	13	2	[redacted]
Santoro, Nanette UMDNJ New Jersey Medical School Department of Obstetrics and Gynecology 185 S. Orange Ave. Newark, NJ 07103-2714	6905	Ph. II/III	4	2	[redacted]
Soules, Michael Department of Obstetrics and Gynecology University of Washington School of Medicine 4225 Roosevelt Way, NE Seattle, WA 98105	6905	Ph. II/III	5	5	[redacted]

Investigator Name/Address	Protocol No.	Type of Study	Center No.	No. of Patients Entered	Subinvestigators
Spratt, Daniel Division of Endocrinology Maine Medical Center Unit # 116 US Route 1 Portland, ME 04102	6905	Ph. II/III	6	4	None
Steinberger, Emil Texas Foundation for Research in Reproductive Medicine 7400 Fannin Street Suite 855 Houston, TX 77054	6905	Ph. II/III	7	3	[redacted]
Steinkampf, Michael Department of Obstetrics and Gynecology University of Alabama 343 Old Hillman Building 618 South 20th Street Birmingham, AL 35233	6905	Ph. II/III	14	1	None
Walmer, David Department of Obstetrics and Gynecology Duke University Medical Center Trent Drive Durham, NC 27710	6905	Ph. II/III	11	2	[redacted]
Wheeler, Carol Department of Obstetrics and Gynecology Women and Infants' Hospital of Rhode Island 101 Dudley St. Providence, RI 2905	6905	Ph. II/III	9	1	[redacted]
Kentenich, Heribert Universitätsklinikum der FU Berlin, Germany	7798	Ph. III	5	1	[redacted]
Neulen, Joseph Klinikum der Albert-Ludwigs-Universität Freiburg Freiburg, Germany	7798	Ph. III	7	1	[redacted]
Thaele, Michael Gemeinschaftspraxis Happel, Thaele, Bühler Saarbrucken, Germany	7798	Ph. III	10	0	None
Hamori, Miklos Gemeinschaftspraxis Bregulla, Hamori, Behrens Erlangen, Germany	7798	Ph. III	3	0	None

Investigator Name/Address	Protocol No.	Type of Study	Center No.	No. of Patients Entered	Subinvestigators
Wiedemann, Ranier GemeinschaftspraxisDr. med. Stuckensen, Wiedemann Wurzburg, Germany	7798	Ph. III	12	6	None
Strowitzki, Thomas Klinikum Großhadern Munchen, Germany	7798	Ph. III	9	1	None
Noss, Ulrich Zentrum für Reproduktionsmedizin Munchen, Germany	7798	Ph. III	8	1	None
Kleinstein, Jürgen Otto-von-Guericke-Universität Magdeburg, Germany	7798	Ph. III	6	4	None
Diedrich, Klaus Medizinische Universität zu Lübeck Lubeck, Germany	7798	Ph. III	2	0	[redacted]
Braendle, Wilhelm Universität Hamburg Hamburg, Germany	7798	Ph. III	1	1	[redacted]
Abad, L. Hospital Virgen de la Arrixaca Murcia, Spain	8297	Ph. III	11	4	[redacted]
Balasch, Juan Hospital Clínic i Provincial Barcelona, Spain	8297	Ph. III	1	6	[redacted]
Barri, P.N. Institut Dexeus, Barcelona, Spain	8297	Ph. III	4	3	[redacted]
Caballero, P. Hospital Ramón y Cajal, Madrid, Spain	8297	Ph. III	6	1	[redacted]
Calaf, J. Hospital de la Santa Creui Sant Pau, Barcelona, Spain	8297	Ph. III	5	6	[redacted]
Cano, I. Hospital Materno-Infantil Carlos Haya, Málaga, Spain	8297	Ph. III	7	1	[redacted]
de Castro, F.J. Hospital Principe de Asturias Alcalá de Henares Madrid, Spain	8297	Ph. III	16	2	None
Duque, J.A. Hospital Miguel Servet Zaragoza, Spain	8297	Ph. III	12	2	[redacted]
Herruzo, A. Hospital Universitario Virgen de las Nieves Granada, Spain	8297	Ph. III	14	2	[redacted]

Investigator Name/Address	Protocol No.	Type of Study	Center No.	No. of Patients Entered	Subinvestigators
Pellicer, A. InstitutoValenciano de Infertilidad Valencia, Spain	8297	Ph. III	2	3	[redacted]
Rodriguez, F.J Hospital de Cruces Baracaldo, Vizcaya, Spain	8297	Ph. III	8	1	[redacted]
Romeu, A. Hospital La Fe, Valencia, Spain	8297	Ph. III	3	2	[redacted]
Ruiz, J.A. Hospital 12 de Octubre, Madrid, Spain	8297	Ph. III	9	3	[redacted]
Santo, J. Hospital La Paz Madrid, Spain	8297	Ph. III	10	2	[redacted]

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19.2. LIST OF INVESTIGATORS AND SUBINVESTIGATORS FOR WHOM DUE DILIGENCE WAS PERFORMED BUT FINANCIAL DISCLOSURE WAS NOT OBTAINED

Investigator Name/Address	Protocol No.	Type of Study	Center No.	No. of Patients Entered	Due Diligence	Reason Why Financial Disclosure Was Not Obtained
Hull, M. University of Bristol Bristol, UK	6253	Ph. II/III	8	2	Letter sent to site requesting completion of disclosure form.	Site notified us of the investigator's death
[redacted] (subinvestigator for Dr. Shoham) Kaplan Hospital Rehovot, Israel	6253	Ph. II/III	4	5	Investigated current location of [redacted]	Investigator retired. Unable to contact.
[redacted] (subinvestigator for Dr. Sara Berga) Department of Obstetrics and Gynecology Magee Women's Hospital Forbes Avenue and Halket St Pittsburgh, PA 15213	6905	Ph. II/III	1	2	Contacted investigative site to obtain current location for [redacted]	Investigator left new location – no forwarding information was known. Attempts to locate continue.
[redacted] (subinvestigator for Dr. Keith Hansen) Department of Obstetrics and Gynecology The Medical College of Georgia 1120 15th Street CJ-134 Augusta, GA 30912	6905	Ph. II/III	12	4	Contacted investigative site to obtain current location for [redacted] Submitted disclosure form to new location.	Investigator not responding to contact attempts. Attempts continue.

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SERONO, INC.
ONE TECHNOLOGY PLACE
ROCKLAND, MA 02370 USA

FACSIMILE TRANSMITTAL SHEET

TO:	FROM:
Archana Reddy Regulatory Project Manager FDA, DRUDP	Lisa S. Mills Serono, Inc.
FAX NUMBER: (301) 827 4267	TELEPHONE NUMBER: (781) 681-2273
PHONE NUMBER: (301) 827 7514	DATE: 8-Oct-04
RE: Luveris NDA 21-322	TOTAL NO. OF PAGES INCLUDING COVER: 7

☐ URGENT ☐ FOR REVIEW ☐ PLEASE COMMENT ☐ PLEASE REPLY ☐ PLEASE RECYCLE

NOTES/COMMENTS:

Hi Archana,

As requested, please find attached copies of the two Form FDA 3542s for Patent 5,767,251 and Patent 5,650,390:

If you need further information, please call me at (781) 681 2273.

Sincerely,

Lisa S. Mills
Associate Director, Regulatory Affairs

10/8/04

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**ODS CONSULT #:**
June 22, 2004	August 30, 2004 **PDUFA DATE:** November 26, 2004	01-0107-1

TO: Daniel Shames, MD
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Archana Reddy
Project Manager
HFD-580

PRODUCT NAME:	**NDA SPONSOR:** Serono, Inc.
Luveris® (Lutropin Alfa for Injection) 75 International Units **NDA #: 21-322**	

SAFETY EVALUATOR: Linda M. Wisniewski, R.N.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Luveris. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name and its associated labels and labeling, must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DDMAC finds the proprietary name Luveris acceptable from a promotional perspective.

/S/

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: July 12, 2004

NDA # 21-322

NAME OF DRUG: **Luveris®**
(Lutropin Alfa for Injection) 75 International Units

NDA HOLDER: Serono, Inc.

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products, to review the proprietary name Luveris®, regarding potential name confusion with other proprietary and established drug names.

PRODUCT INFORMATION

Luveris® (lutropin alfa for injection) is a sterile lyophilized powder composed of recombinant human luteinizing hormone, r-hLH. It is intended for co-administration with follitropin alfa as a subcutaneous injection after reconstitution with Sterile Water for Injection, USP. It is administered with folitropin alfa to stimulate development of a competent follicle and to indirectly prepare the reproductive tract for implantation and pregnancy. Each vial contains 82.5 International Units of lutropin alfa. It is indicated for concomitant administration with r-hFSH for the induction of ovulation in infertile women with severe LH deficiency. The dose of Luveris should be individualized for each patient. It is recommended that the initial dose of Luveris in the first cycle of treatment be 75 International Units with r-hFSH, administered subcutaneously. Luveris and rh-FSH should be administered daily until adequate follicular development is indicated by serum estradiol and ovary ultrasonography. Treatment duration should not normally exceed — days unless signs of imminent follicular development are present. Reconstitution instructions direct the patient to dissolve the contents of one vial of Luveris in 1 mL Sterile Water for Injection, USP. The reconstituted Luveris solution is then injected into the r-hFSH powder and gently mixed. Luveris will be supplied in a sterile, lyophilized single dose vial containing 82.5 International Units r-hLH, which delivers 75 International Units r-hLH, after reconstitution with the diluent.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to "Luveris" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted.[4] The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Luveris." Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. The members of this panel include DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Luveris, acceptable from a promotional perspective.
2. The Expert Panel identified nine proprietary names as having the potential for confusion with Luveris. These products are listed in Table 1 (see page 4).
3. Similarly, through independent review, the name [redacted] was identified as having potential for orthographic similarities to Luveris. This product is listed in Table 1 (see page 4).

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, Drugs@fda, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/main/trademarks.htm

[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Table 1. Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

[redacted]			
Lavoris	Zantrate Oral rinse.	Rinse for 30 seconds twice daily.	LA/SA
Luxacor	Fenofibrate Capsules: 50 mg, 100 mg, 150 mg, 160 mg	Initial dose of 50 mg to 160 mg per day. Maximum dose of 160 mg daily.	LA
[redacted]			
Levitra	Vardenafil Hydrochloride Tablets 2.5 mg, 5 mg, 10 mg, and 20 mg.	5 mg to 20 mg once daily.	LA
[redacted]			
Lovenox	Enoxaparin Sodium Injection 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 90 mg/0.6 mL, 120 mg/0.8 mL, 150 mg/mL, 300 mg/3 mL	30 mg to 40 mg Subcutaneously every 12 or 24 hours 1 mg to 1.5 mg/kg Subcutaneously q12 hours	LA
Lanoxin	Digoxin Injection: 0.1 mg/mL and 0.25 mg/mL Tablet: 0.125 mg and 0.25 mg	0.125 mg to 1.25 mg daily with divided doses.	LA
[redacted]			

* Frequently used.
** L/A (look-alike), S/A (sound-alike)
NOTE: **This review contains proprietary and confidential information that should not be released to the public.**

B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic database that is in the final stages of development for DMETS. The entered search term is converted into its phonemic representation before it runs though the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. The results from the Luveris queries did not indicate any additional product names that had strong phonetic or orthographic similarities to the input text.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Luveris, the primary concerns raised were related to potential confusion with the currently marketed products: Lavoris, Luxacor, Lovenox, and Lanoxin; and the proposed proprietary names [ ], and [ ]

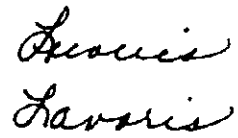
1.

2. [

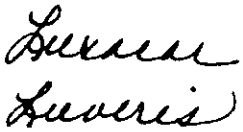
]

*** NOTE: This review contains proprietary and confidential information that should not be released to the public.***

3. Lavoris may look and sound similar to Luveris. Lavoris is an over-the-counter brand of mouthwash. Both names contain letters that may look and sound similar (luv vs. lav and oris vs. eris) (see below). Similar spelling and identical character length (6 letters) contribute to phonetic similarities and orthographic similarities . However, there are characteristics that may help to differentiate these two products; these include dose (75 International Units to 225 International Units vs. mouthful), dosage form (for injection vs. oral rinse), frequency of administration (once daily vs. twice daily), route of administration (subcutaneous vs. orally), and indication (ovulation induction in infertile women with severe LH and FSH deficiency vs. breath freshener). Despite the orthographic and phonetic similarities, the product characteristics will help to differentiate these two products.



4. Luxacor may look similar to Luveris when scripted. Luxacor is indicated as adjunctive therapy to diet in adult patients with primary hypercholesterolemia or mixed dyslipidemia. Both names begin with letters that may look similar (lux vs. luv), particularly if the cross bar for the 'x' is not clearly scripted. The rest of the letters are different (acor vs. eris), however, their orthographic presentation may look similar (see below). There are product characteristics that may help to differentiate them, such as dose (75 International Units to 225 International Units vs. 50 mg to 160 mg), strength (75 International Units vs. 50 mg, 100 mg, 150 mg, and 160 mg) dosage form (for injection vs. capsules), route of administration (subcutaneous vs. oral), and indication of use (ovulation induction vs. hypercholesterolemia and dyslipidemia). Thus, the product characteristics will help to differentiate the two products and help to minimize error.



5. [redacted]

[redacted]

*** NOTE: This review contains proprietary and confidential information that should not be released to the public.***

6. Levitra may look similar to Luveris when written. Levitra is indicated in men with erectile dysfunction. Both names begin with letters that look similar (lev vs. luv) and contain five of the same letters (levir), but with different placement. However, the upstroke for the 't' in Levitra may help to differentiate the two names when scripted (see below). Although both drugs are dosed once daily, there are some differentiating product characteristics, such as dose (75 International Units to 225 International Units vs. 2.5 mg, 5 mg, 10 mg, and 20 mg), strength (75 International Units vs. 2.5 mg, 5 mg, 10 mg, and 20 mg), dosage form (for injection vs. tablet), route of administration (subcutaneous vs. oral), and indication of use (ovulation induction vs. erectile dysfunction). The product characteristics will help to differentiate Levitra and Luveris.

Levitra
Luveris

7. C

J

8. Lovenox may look similar to Luveris when scripted. Lovenox is indicated for the prevention of deep vein thrombosis (DVT) following knee, hip or abdominal surgery, unstable angina and myocardial infarction. Both names begin with letters that look similar when scripted (love vs. luve and enox vs. eris) (see page 8). Although there are orthographic similarities and both products are injectables that may be administered daily, there are product characteristics that may help to differentiate them. These include characteristics such as dose (75 to 150 International Units vs. 30 mg to 40 mg or 1 mg to 1.5 mg/kg), strength (75 International Units/vial vs. 30 mg/0.3 mL, 40 mg/0.4 mL,
60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 90 mg/0.6 mL, 120 mg/0.8 L, 150 mg/mL, 300 mg/3 mL), and indication of use (ovulation induction vs. prevention of deep vein thrombosis (DVT). Thus, the strengths and the conditions of use will help to differentiate these two products and help to minimize error.

Lovenox
Luveris

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9. Lanoxin may look similar to Luveris when scripted. Lanoxin is used to increase cardiac output in patients in heart failure and as an antiarrhythmic in the treatment of atrial fibrillation and atrial flutter. Both names contain letters that may look similar (lan vs. luv). The rest of the letters (eris vs. oxin) may look similar. There are some differentiating product characteristics, such as dose (75 to 150 International Units vs. 0.125 mg to 1.25 mg), strength (0.25 mg/mL, 0.125 mg and 0.25 mg vs. 75 International Units), route of administration (subcutaneously vs. intravenously and oral), and indication of use (ovulation induction vs. heart failure and arrhythmias). The dose, strength, and route of administration will help to minimize confusion between these two products.

Luveris. Lanoxin

10. [redacted]

III. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name, Luveris, provided that only one name Luveris or —— * is approved. These names should not co-exist in the marketplace due to their orthographic similarity and numerous similar product characteristics. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name and its associated labels and labeling, must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

B. DDMAC finds the proprietary name Luveris acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Linda Wisniewski, RN
Safety Evaluator
Division of Medication Errors and Technical Support

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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/

Denise Toyer
10/8/04 04:49:44 PM
DRUG SAFETY OFFICE REVIEWER
Signing for Carol Holquist, Director DMETS

8 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

8-30-04

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: October 8, 2004

To: Pamela Williamson Joyce, RAC Vice President, Regulatory Affairs and Quality Assurance Cc: Lisa Mills Associate Director, Regulatory Affairs	**From:** Archana Reddy, M.P.H. Regulatory Project Manager
Company: Serono, Inc.	Division of Division of Reproductive and Urologic Drug Products
Fax number: 781-681-2924	**Fax number:** 301-827-4260
Phone number: 781-681-2273	**Phone number:** 301-827-4260

Subject: Approval letter for NDA 21-322 (Luveris)

Total no. of pages including cover: 21

Comments:

Document to be mailed: ☐ YES ☑ NO

Luveris Division Director's Memorandum

RE: Complete Response to a Not-Approvable Action.

For:	**NDA 21-322**
From:	**Daniel A. Shames MD** **Director,** **Division of Reproductive and Urologic Drug Products** **CDER/FDA**
Complete Response Submitted:	**May 25th, 2004**
PDUFA Goal Date:	**November 26th, 2004**
Date of Memorandum:	**October 6th, 2004**
To:	**File**
Drug:	**Luveris (lutropin alfa for injection)**
Sponsor:	**Serono Laboratories, Inc**
Indication:	**Luveris (lutropin alfa for injection), concomitantly administered with Gonal-f for injection, is indicated for the stimulation of follicular development in infertile hypogonadotropic women with profound LH deficiency (LH < 1.2 IU/L). A definitive effect on pregnancy in this population has not been demonstrated. The safety and effectiveness of concomitant administration of Luveris with any other preparation of recombinant FSH or urinary human FSH is unknown.**
Dosage/Form/Route:	**75 IU sterile lyophilized powder to be reconstituted with 1 ml Sterile Water for Injection. A 75 IU dose is concomitantly administered with Gonal-f via subcutaneous route as two separate injections.**

1.0 Clinical and Regulatory Background

The first significant contact between the Agency and the Sponsor occurred at a pre-IND meeting on May 21, 1992. At this meeting, a discussion took place regarding the use of recombinant luteinizing hormone (r-hLH) (Luveris) for the treatment of women with WHO group I anovulation (idiopathic hypogonadotropic hypogonadism). This is a rare condition estimated by the Sponsor to be 14,740 cases per year in the United States. The sponsor also proposed that Luveris should be considered as an orphan drug. A request for orphan status, subsequently approved, was submitted January 14, 1994.

Luveris is formulated as a lyophilized powder that contains a heterodimeric glycoprotein whose alpha and beta subunits are very similar to pituitary-derived luteinizing hormone (LH).

At the pre-IND meeting, it was agreed that two identical clinical studies of equal size (32 patients in each study) using the same protocol [one in the United States (Study 6905) and one in Europe (Study 6253)] would be performed in women with WHO group I anovulation.

Women with WHO group I anovulation are amenorrheic, with little or no endogenous estrogen activity who do not respond with withdrawal bleeding when suitable progesterone is administered. Studies 6905 and 6253 were designed to support an application for ovulation induction in these hypogonadotropic women. The Sponsor submitted only one protocol for a clinical trial to IND 44,108 on December 8, 1993 to be conducted in the United States (Study 6905). Study 6905 was entitled "An open, randomized, dose-finding (using 25IU and 75 IU of LH) multi-center study to determine the minimal effective dose and to assess the safety of r-hLH to support r-FSH – induced follicular development in anovulatory women with hypogonadotropic hypogonadism." No mention of the European study protocol was made in the IND, and this protocol was not submitted to the Agency prior to the completion of the European study. Two significant revisions were made by the Sponsor in the "Inclusion Criteria" of Study 6905 to ensure that the study populations more closely matched the endocrine profile of the hypogonadotropic patients treated in clinical practice in the U.S. The protocol amendment containing these changes to study 6905 was submitted on July 20, 1994 before the start of the study. These protocol changes were:

1. The need to have a negative progesterone challenge test was replaced by the requirement for a serum estradiol concentration of less than 60 pg/mL.
2 The requirement for serum FSH and LH levels below 5 IU/L was replaced by the requirement to be at or below the 50th percentile of normal range for the follicular phase established. (The central laboratory for hormonal parameters for Study 21415 was reported as [ ]

In contrast to Study 6905, Study 6253 (the European study) had an inclusion criteria of a serum LH less than 1.2 IU/L. Therefore, the populations of women with hypogonadotropic hypogonadism based on endogenous levels of LH were different for the two studies. The primary endpoint for both studies was follicular development as defined by three co-parameters: pre-ovulatory estradiol levels, ultrasound follicular measurement, and mid-luteal progesterone levels).

A pre-NDA briefing document was submitted on June 12, 1998, including data from Study 6905 and Study 6253. The proposed indication was "treatment of women with chronic anovulation due to hypogonadotropic hypogonadism (H.H.)." The Sponsor requested that the Agency confirm that the data from U.S. Study (6905) and European Study (6253) were adequate for filing and approval of an NDA. The primary efficacy parameter for both studies 6905 and 6253 was "follicular development" as defined by three co-primary endpoints (follicle size as measured on ultrasound, pre-ovulatory serum estradiol levels, and mid-luteal serum progesterone levels).

The Sponsor's analysis demonstrated that in Study 6253, 75 IU of Luveris was numerically better than 25 IU of Luveris or placebo for follicular development in women with LH <1.2 IU/L. In Study 6905, however, the Sponsor's analysis demonstrated that both 25 IU of Luveris and 75 IU of Luveris were effective for follicular development in women with hypogonadism whose LH levels were less than 13.3 IU/L.

The Division's analysis of Study 6905 demonstrated that 25 IU of Luveris was numerically superior to 75 IU of Luveris and that placebo was as efficacious as 75 IU of Luveris. Therefore, in the opinion of the Division, Luveris® was not demonstrated to be effective in treating hypogonadotropic hypogonadism as "usually diagnosed in the United States" (per the Sponsor). Furthermore, Study 6253 (the European study) revealed that (in contrast to the United States study) 75 IU of Luveris was numerically better than either 25 IU of Luveris or placebo. An additional subset analysis of patients in Study 6905 with an LH of less than 1.2 IU/L failed to confirm the findings of Study 6253.

In an August 11, 1998 teleconference with the sponsor, the following conclusions of the Division were communicated:
1.The results of the studies were different.
2.Neither study showed a significant difference in efficacy of the proposed endpoints. The most positive finding was the dose-related trend in the ITT analysis of Study 6253.
3.More data would be needed before the NDA would be fileable.

On October 21, 1998, the fileability of the proposed NDA was discussed with the Director, Office of Drug Evaluation III and the Deputy Director, Center for Drug Evaluation and Research who agreed that if the NDA were submitted, it would not be fileable.

The Sponsor provided a supplemental pre-NDA meeting package on November 18, 1998 containing new data from two additional clinical trials carried out in Europe. Study 7798 was conducted in Germany on a profoundly LH deficient population (LH less than 1.2 IU/L) while Study 8297 was conducted in Spain in a moderately LH deficient population (LH below or within the normal range). These two new clinical trials, Studies 7798 and 8297, were not designed to determine the minimal effective dose, had different patient populations, and did not use doses less than 75 IU.

The Deputy Director of ODE III and the Division met again with the Sponsor on November 30, 1998. The discussions included the following additional points:
1. A trend test was proposed by the sponsor as the confirmatory statistical tool for efficacy assessment; step down doses were studied, beginning with the highest dose to

demonstrate significance in order to avoid multiple comparison problems. The Agency considered these trend tests to be exploratory tests and appropriate for trials providing substantial evidence.
2. The Sponsor expressed their position that the 75 IU was the proposed dose because in their view it was the optimal dose.

In a communication with the Division on December 16, 1998, the Sponsor stated that data Studies 6253 and 7798 would provide the primary evidence for it's NDA.

On February 23, 1999, another teleconference with the Sponsor was held to discuss the fileability of its proposed NDA. The following points were discussed:
1. The efficacy data included insufficient numbers of subjects to support fileability.
2. The primary endpoint should be the ovulation rate in a one-month treatment cycle.
3. The Division stated that the Sponsor should conduct a phase 3 clinical trial with wider inclusion criteria (for patient populations typically considered for Luveris treatment) comparing 75 IU of Luveris with placebo in patients with LH levels less than 5 IU/L, including a significant number of patients with a screening LH less than 1.2 IU/L all of whom desired pregnancy.

The Sponsor proposed a new protocol (21008) for a Phase III clinical trial. The protocol was submitted to the IND (44,108) on March 22, 1999. A teleconference with the Sponsor was held on May 3, 1999. The Division stated that:
1. The proposed estradiol and progesterone levels for follicular development would be re-evaluated and a valid argument for the proposed levels would be subject to review.
2. The estimated success rate would be recalculated for each treatment group using the new criteria since the progesterone (and possibly) estradiol group used to determine treatment success may be changed.

A pre-NDA meeting was held with the Sponsor on December 12, 2000 to discuss the completion of an additional Phase III study that the Division had requested (Study 21008). At that meeting the Division acknowledged that Study 21008 would be an acceptable double-blind, placebo-controlled, randomized trial. The Division did discuss with the Sponsor that serum LH levels would be used to stratify analyses of the data.

NDA 21-322 was received on May 1, 2001 and filed on June 30, 2001. Study 21008 was a randomized, double-blind, placebo-controlled multi-center study conducted in 25 multinational centers. The Division had made a recommendation to the Sponsor that ovulation rate (as determined by the percentage of subjects achieving a mid-luteal progesterone level of greater than 10 ng/ml) should be the primary endpoint. The Sponsor chose follicular development as previously defined as the primary endpoint. In addition, the review staff was concerned that women who had their cycle cancelled because of the risk of ovarian hyperstimulation syndrome were included as successes.

The Sponsor's evaluable patient analysis of Study 21008 demonstrated that 67% of patients receiving 75 IU of Luveris achieved follicular development compared to 20% of patients receiving placebo. This analysis counted as successes treatment cycles cancelled for the risk of development of ovarian hyperstimulation syndrome (OHSS).

The Division's intent-to-treat (ITT) analysis of Study 21008, (which counted cycle cancellations as failures), demonstrated that 38% of patients receiving 75 IU of Luveris® achieved follicular development compared to 8% of patients receiving placebo. Of note, the Sponsor had expected that an effective dose of Luveris would result in a 90% follicular development rate in Luveris treated patients. Both analyses of the primary endpoint in Study 21008 fell short of this expectation.

The initial Medical Officer Review was completed on February 25, 2002 evaluating the five submitted clinical trials (Studies 6905, 6253, 21008, 7798, and 8297) in which a total of 173 subjects participated. The Medical Officer concluded that the application for should not be approved, as the clinical data did not demonstrate efficacy of Luveris. Furthermore, the Medical Officer judged that none of the five clinical trials demonstrated that the treatment effect of Luveris was clinically or statistically significant.

The Division's objections to approval of this NDA were:

1. The Sponsor utilized "follicular development" as the primary efficacy endpoint in Studies 21008 and 6253 as opposed to ovulation.
2. The Division believed that although both follicular development and ovulation are surrogates for pregnancy (the clinically meaningful outcome), ovulation is more temporally proximate to pregnancy and therefore more appropriate as a surrogate.
3. In its analysis of the data, the Sponsor included patients who were cancelled due to a risk of ovarian hyperstimulation syndrome. The division believed that this was inappropriate. The Division's re-analysis of the data using the Sponsor's criteria for follicular development, and counting patients who were cancelled because of a risk of ovarian hyperstimulation syndrome as a failures, resulted in a p value of 0.063 (study 21008). Therefore, this result was not statistically significant.

It was the opinion of the Division that even with "follicular development" as a surrogate endpoint, there was insufficient evidence to conclude that treatment with Luveris 75 IU was significantly different from placebo.

The Acting Deputy Division Director concurred with the Not Approvable decision on February 28, 2002 and a Not Approvable action letter was sent on March 1, 2002.

A meeting to discuss the Not Approvable action letter was held with the Sponsor on May 10, 2002. At this meeting, the Division recommended that the Sponsor propose a new phase III trial. This trial would include one or two doses lower than the proposed 75 IU dose. The Sponsor proposed instead to submit an open-label, non-randomized, extension study (21415) that used patients recruited in study 21008. The data from study 21415 included additional ovulation and pregnancy data.

The following comments were relayed to the Sponsor at the May 10, 2002 meeting:

1. The Division stated that the extension Study 21415 was unacceptable as a "pivotal study" as it was not placebo controlled and was unblinded.
2. The Division requested that the Sponsor provide full study report for the 75 IU group (Study 21415).

3. The Division pointed out that the Sponsor had agreed previously with the Division that the requirement for efficacy of Luveris would be that Luveris is more effective than placebo.

The Division conveyed the following two options for moving forward to the Sponsor at this May 2002 meeting:
1. The Sponsor could appeal the Not Approvable action to the ODE III immediate office.
2. The Sponsor could submit a protocol utilizing ovulation rates as the primary endpoint. In addition, the Division stated that the Sponsor should propose that multiple doses be evaluated, including one or two doses lower than the 75 IU, as well as the 75 IU dose.

A was held with the Sponsor on January 9, 2003 to continue the discussion on the Not Approvable action letter issued on March 1, 2002. The Division reiterated the comments from the May 2002 meeting and relayed the following additional options and comments to the Sponsor:
1. An advisory committee meeting could be convened over a two-day period in approximately six months to discuss assisted reproductive technology products in general on one day and the not approvable action for Luveris on another.
2. The Sponsor can conduct another phase III study as previously discussed.
3. The Sponsor was also asked to formally submit Study 21415 to the NDA for review by the Division.

The Sponsor formally submitted Study 21415 on April 28, 2003. The medical reviewer concluded that study 21415 was a post-hoc, non-randomized, open-label study that was inadequate to make any efficacy conclusions concerning Luveris (See Medical Officer's review of finalized September 9, 2003). This information was conveyed to the sponsor.

The Sponsor then opted to have the application discussed before the Advisory Committee. Luveris was discussed on September 30, 2003, the second day of a two-day meeting of the Reproductive Health Advisory Committee. After hearing presentations from experts in Reproductive Endocrinology on the subject of female hypogonadotropic hypogonadism as well as the presentations from the Division and the Sponsor on the efficacy data for Luveris, the Committee was asked to discuss the application and vote.

2.0 Results of the Advisory Committee Meeting

The Committee voted 11 to 3 that the Sponsor's data demonstrated efficacy for follicular development. In addition, the Division Director interpreted the advisory committee proceedings as indicating that for this orphan population (WHO I), follicular development would be an appropriate surrogate for pregnancy. The committee did indicate that for other larger populations clinical pregnancy (including fetal heartbeat) should be the endpoint in trials for infertility drugs. In addition, following the Advisory Committee Meeting, the Division committed to reassessing Study 21415 in its process of addressing Sponsor's request for reconsideration of the Division's Not Approvable decision for NDA 21-322.

A Type A meeting was held with the Sponsor on January 9, 2004 to discuss the deliberations of the Advisory Committee held in September 2003. The Division Director

agreed to review the application, the regulatory history, scientific data, and the Advisory Committee transcripts and make a decision regarding approvability.

3.0 Regulatory and Scientific Conclusions Post Advisory Committee Meeting

The Director of the Division considered the deliberations and recommendations from the Advisory Committee and discussion points raised by the sponsor in various communications and concluded that induction of follicular development is an acceptable surrogate efficacy endpoint for clinical trials conducted in infertile, profoundly LH-deficient women with hypogonadotropic hypogonadism. The Director further concluded that the results from Studies 21008 and 6253 provide substantial evidence that Luveris 75 IU, when administered concomitantly with FSH, induces follicular development in this population of infertile women. These studies however, do not demonstrate a positive effect on clinical pregnancy rate. Study 21415 evaluated titratable FSH dosing with the dose of Luveris fixed at 75 IU and demonstrated a 36% clinical pregnancy rate after one cycle. While reassuring, this finding is not definitive because there was no placebo comparator group in Study 21415, and the finding has not been replicated in a second trial.

The Director believes that infertility in the context of hypogonadotropic hypogonadism and profound LH deficiency (WHO I) is a serious condition with very limited options for pregnancy. Therefore, NDA 21-322 should be considered under the accelerated approval regulations, Subpart H, 21 CFR 314.510, acknowledging that induction of follicular development is a surrogate endpoint that is reasonably likely to predict the clinical benefit of pregnancy in infertile, profoundly LH-deficient women with hypogonadotropic hypogonadism. Approval of NDA 21-322 under 21 CFR 314.510 would be subject to the requirement that the sponsor conduct an adequate and well-controlled postmarketing study to verify and describe the clinical benefit of Luveris with respect to pregnancy. Furthermore, under 21 CFR 314.530, FDA may withdraw marketing approval for Luveris if a postmarketing study fails to verify clinical benefit or if the Sponsor fails to perform the required postmarketing study with due diligence.

In a letter dated April 30, 2004 the Director relayed the above information to the sponsor and offered the following advice:

"If you wish to pursue approval under Subpart H, we will accept the following components as a complete response to the Not Approvable letter of March 1, 2002. The request in the Not Approvable letter to conduct a pre-approval placebo-controlled, dose-ranging study to evaluate ovulation induction in hypogonadotropic hypogonadal women with profound LH deficiency and infertility is not necessary for approval under Subpart H as described above. Previously submitted information may be incorporated by reference into your complete response. Before your application may be approved, you will need to submit the following:

1. The final study report for Study 21415;
2. Your proposed protocol, to confirm clinical benefit, for a randomized, double-blind, placebo-controlled postmarketing study with pregnancy as the primary endpoint in profoundly LH-deficient infertile women with hypogonadotropic hypogonadism when Luveris is concomitantly administered with titratable FSH. Prior to approval,

agreement must be reached on the overall study design and analysis plan, as well as your proposed times for initiation of patient enrollment, completion of enrollment, and submission of the final study report to the division;

3. Draft professional labeling that:

Specifies in the INDICATIONS AND USAGE section that Luveris, administered with follitropin alfa for injection, is indicated for induction of follicular development in hypogonadotropic hypogonadal infertile women with severe LH (1.2 IU/L) deficiency, and that a definitive effect on pregnancy in this population has not been demonstrated; and

Includes a description of the design and major findings of Studies 21008 and 6253 in the CLINICAL STUDIES subsection of the CLINICAL PHARMACOLOGY section; for each study, the results of the analysis of the composite primary efficacy endpoint of follicular development (follicle size, pre-ovulatory estradiol level, and mid-luteal phase P4 level) should be presented (a) with cycle cancellation for the risk of ovarian hyperstimulation syndrome (OHSS) counted as a success, and (b) with cycle cancellation for the risk of OHSS counted as a failed response."

After some preliminary communications regarding the above issues, Serono submitted the above requested materials on July 23, 2004. Negotiations regarding the Labeling and the Phase 4 protocol continued until October 2004 when the Director believed that satisfactory agreement had been reached on all outstanding issues.

Regulatory Action

On October 8th , 2004 an approval letter for NDA 21-322 was issued under Subpart H, 21 CFR 314.510, for Luveris 75 IU for the following indication:

Luveris (lutropin alfa for injection), concomitantly administered with Gonal-f (follitropin alfa for injection) is indicated for the stimulation of follicular development in infertile hypogonadotropic women with profound LH deficiency (LH < 1.2 IU/L). A definitive effect on pregnancy in this population has not been demonstrated. The safety and effectiveness of concomitant administration of Luveris with any other preparation of recombinant FSH or urinary human FSH is unknown.

Daniel A. Shames MD
Director, Division of Reproductive and Urologic Drug Products
CDER/FDA

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

/s/

Margaret Kober
10/8/04 01:59:17 PM
CSO
entered for Dr. Shames's signature

Daniel A. Shames
10/8/04 02:05:22 PM
MEDICAL OFFICER

65 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

16-7-94

2004

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA: 21-322	Efficacy Supplement Type SE-	Supplement Number N/A	
Drug: Luveris® (lutropin alfa for injection)		Applicant: Serono, Inc.	
RPM: Archana Reddy, M.P.H.		HFD-580	Phone # 7-7514

Application Type: (X) 505(b)(1) ( ) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	(X Standard ( ) Priority
• Chem class (NDAs only)	3s
• Other (e.g., orphan, OTC)	Orphan
❖ User Fee Goal Dates	November 26, 2004
❖ Special programs (indicate all that apply)	( ) None Subpart H (X) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	( ) Paid UF ID number
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	(X) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No

• **This application is on the AIP**	( ) Yes (X) No
• **Exception for review (Center Director's memo)**	N/A
• **OC clearance for approval**	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has	( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).*	( ) Yes ( ) No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	No
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	X (May 16, 2001)

❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	Not Approvable (March 1, 2002)
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	October 5, 2004
• Original applicant-proposed labeling	April 30,2004
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC (August 30, 2004) DMETS (May 17, 2001, October 8, 2004)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	June 11, 2004, September 29,2004
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	X
• Documentation of discussions and/or agreements relating to post-marketing commitments	X
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	X (5/3/99)
• Pre-NDA meeting (indicate date)	X (7/10/98, 12/12/00)
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	X
❖ Advisory Committee Meeting	
• Date of Meeting	September 30, 2003
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	X

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	X (Medical Team Leader- 10/08/04) X (Division Director- 10/07/04)
❖ Clinical review(s) *(indicate date for each review)*	10/06/04, 3/01/02
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	X (See Medical Officer's review)
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	X
❖ Biopharmaceutical review(s) *(indicate date for each review)*	X
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X
• Bioequivalence studies	N/A
❖ CMC review(s) *(indicate date for each review)*	X (10/7/04, 02/28/02)
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	X (05/1/01)
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	X (02/11/02)
❖ Facilities inspection (provide EER report)	Date completed: July 7, 2004 **(X)** Acceptable **( )** Withhold recommendation
❖ Methods validation	**( )** Completed **( )** Requested **(X)** Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	X (02/11/02)
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

NDA: 21-322
Drug: Luveris® (lutropin alfa for injection)
Sponsor: Serono, Inc.

Nonclinical Inspection Summary

This new drug application did not require a nonclinical inspection.

NDA: 21-322
Drug: Luveris® (lutropin alfa for injection)
Sponsor: Serono, Inc.

Pre-Approval Safety Conference

There was no pre-approval safety conference held for this new drug application.

NDA: 21-322
Drug: Luveris® (lutropin alfa for injection)
Sponsor: Serono, Inc.

Demographic Worksheet

A demographic worksheet is not required. This is not a new molecular entity.

NDA: 21-322
Drug: Luveris® (lutropin alfa for injection)
Sponsor: Serono, Inc.

Risk Management Plan

A risk management plan was not required for this new drug application.

NDA: 21-322
Drug: Luveris® (lutropin alfa for injection)
Sponsor: Serono, Inc.

Application Integrity Policy

This new drug application was not subject to the AIP.

NDA: 21-322
Drug: Luveris® (lutropin alfa for injection)
Sponsor: Serono, Inc.

User Fee Information

This new drug application was granted orphan drug designation in 1994. Therefore, this NDA application does not require a user fee (exception).

NDA: 21-322
Drug: Luveris® (lutropin alfa for injection)
Sponsor: Serono, Inc.

Post Marketing Commitments

This new drug application is being approved with the following post marketing commitment:

1. The sponsor commits to conduct a Phase IV confirmatory clinical study to determine the effect of Luveris® on time to clinical pregnancy.

The following is the timeline for this commitment:

Protocol submission: Accomplished in the October 5, 2004 submission
Study start: Within one year of the date of receipt of this action letter
Final Report Submission: Within 6 months of the study completion

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-322 /SE N/A -

Drug Luveris™ (lutropin alfa for injection) Applicant Serono, Inc.

RPM Archana Reddy, M.P.H. Phone 301-827-5424

X505(b)(1)
☐505(b)(2) Reference listed drug

☐Fast Track ☐Rolling Review Review priority: ☒ S ☐P

Pivotal IND(s) IND 44,108

Application classifications:
Chem Class 3S
Other (e.g., orphan, OTC) Orphan

PDUFA Goal Dates:
Primary March 1, 2002
Secondary May 1, 2001

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ☐ User Fee Paid
  X User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption

- Action Letter..... ☐AP ☐ AE ☒NA

- Labeling & Labels
  FDA revised labeling and reviews..... N/A
  Original proposed labeling (package insert, patient package insert) ..... See Labeling Section (4/30/01)
  Other labeling in class (most recent 3) or class labeling..... None
  Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) X No
  Immediate container and carton labels ..... See Labeling Section
  Nomenclature review ..... See Nomenclature Review

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is X is not on the AIP.
  Exception for review (Center Director's memo)..... N/A
  OC Clearance for approval..... N/A

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ☐ Materials requested in AP letter

- Post-marketing Commitments
  - Agency request for Phase 4 Commitments _____
  - Copy of Applicant's commitments _____

- Was Press Office notified of action (for approval action only)? ☐ Yes ☐ No
  - Copy of Press Release or Talk Paper _____

- Patent
  - Information [505(b)(1)] X
  - Patent Certification [505(b)(2)] N/A
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)] X

- Exclusivity Summary X

- Debarment Statement X

- Financial Disclosure
  - No disclosable information _____
  - Disclosable information – indicate where review is located X (See Financial Disclosure Memo)

- Correspondence/Memoranda/Faxes X (See meeting minutes and agency correspondence section)

- Minutes of Meetings X
  - Date of EOP2 Meeting 5/3/99
  - Date of pre NDA Meeting 7/10/98, 12/12/00
  - Date of pre-AP Safety Conference N/A

- Advisory Committee Meeting N/A
  - Date of Meeting N/A
  - Questions considered by the committee N/A
  - Minutes or 48-hour alert or pertinent section of transcript N/A

- Federal Register Notices, DESI documents N/A

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) X

- Clinical review(s) and memoranda X
- Safety Update review(s) X
- Pediatric Information
  X Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  Pediatric Page..... _____
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted X Not Applicable
- Statistical review(s) and memoranda X
- Biopharmaceutical review(s) and memoranda..... X
- Abuse Liability review(s) ..... N/A
  Recommendation for scheduling ..... N/A
- Microbiology (efficacy) review(s) and memoranda ..... N/A
- DSI Audits X
  XClinical studies ☐ bioequivalence studies ..... See DSI audit section

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CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- CMC review(s) and memoranda X
- Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A
- DMF review(s) ..... N/A
- Environmental Assessment review/FONSI/Categorical exemption X
- Micro (validation of sterilization) review(s) and memoranda X
- Facilities Inspection (include EES report)
  Date completed Pending (4/4 sites complete) ..... X Acceptable ☐ Not Acceptable
- Methods Validation ..... Completed X Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Pharm/Tox review(s) and memoranda X

- Memo from DSI regarding GLP inspection (if any) ..... N/A
- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report ..... N/A

Appears This Way
On Original

NDA: 21-322
Drug: Luveris® (lutropin alfa for injection)
Sponsor: Serono, Inc.

Public Communications

This new drug application was not subject the subject of Press Office communications.

NDA 21-322
Luveris (lutropin alfa for injection) 75 I.U.
Serono, Inc.

Abuse Liability Review

This product does not require an abuse liability review.

NDA: 21-322
Drug: Luveris® (lutropin alfa for injection)
Sponsor: Serono, Inc.

Controlled Substance Staff Review

This new drug application was not the subject of a controlled substance staff review.

NDA: 21-322
Drug: Luveris® (lutropin alfa for injection)
Sponsor: Serono, Inc.

Special Programs

This new drug application has been granted accelerated approval under Subpart H (21 CFR 314.510).

NDA 21-322
Luveris (lutropin alfa for injection) 75 I.U.
Serono, Inc.

Federal Register Notices

This application was not the subject of any Federal Register Notices.

AR
2/07/02

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

8/26/04

NDA 21-322

ADVICE LETTER

Serono, Inc.
Attention: Pamela Williamson Joyce, RAC
Vice President, Regulatory Affairs and Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

Please refer to your April 30, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luveris® (lutropin alfa for injection).

We also refer to your correspondence dated April 30, 2004, containing a proposal for a Phase 4 study to confirm the efficacy of Luveris®.

On July 23, 2004, you responded to our July 8, 2004 Advice letter. In your response, you concurred with the Division's recommendations for items 3 – 7, 11, 12, 14, and 15 as listed in our July 8, 2004 letter. You have revised the Phase 4 protocol to incorporate these changes. Listed below are the disputed recommendations from the Division's July 8, 2004 letter, summation of your discussion points on these recommendations, and further comments from the Division.

1. July 8, 2004 Advice letter, item 1 –"We recommend that this study be designed to look for the lowest effective dose and that it evaluate a dose of Luveris® lower than 75 IU in addition to the 75 IU dose".

   - **Sponsor response: The sponsor does not concur that there is a need to study a "lower" dose of Luveris®. Their position is that the results of the studies conducted to date support the 75 IU as the appropriate therapeutic dose.**

   Division's response to Serono's July 23, 2004 letter (item 1): Sub-group analysis from Study 6905 (one of the two dose finding studies) suggested efficacy of a 25 IU dose of Luveris® in hypogonadotropic hypogonadal patients with a serum LH $\leq$ 1.2 IU. The Division recognizes that the number of patients in this subgroup analysis was small and not statistically significant; nevertheless the suggestion of possible efficacy of a 25 IU dose in this analysis was apparent. Serono's representation that 75 IU is effective and lower doses do not need to be studied does not negate the possibility that a lower effective dose demonstrating clinical comparability (from both a safety and efficacy standpoint) may exist. Serono has not presented any additional clinical evidence that would refute the need to examine a lower

dose. In fact, there is literature support that too much LH may be as detrimental to a cycle as too little.[1] Therefore, the proposed Phase 4 study should evaluate the lowest effective dose. The Division continues to recommend that Serono study at least one dose lower than 75 IU of Luveris®.

[1]Tesarik J, Mendoza C., "Effects of exogenous LH administration during ovarian stimulation of pituitary down-regulated young oocyte donors on oocyte yield and developmental competence." *Hum Reprod.* 2002; 17(12):3129-37.

2. July 8, 2004 Advice letter, item 2 – "We recommend that the primary efficacy analysis be an intent-to-treat analysis of time from randomization to the occurrence of a clinical pregnancy, recognized as a gestational sac with fetal heart motion on vaginal ultrasound at 6 weeks post-embryo transfer. We recommend a two-sided 95% or one-sided 97.5% confidence interval analysis of the difference. To demonstrate efficacy, we recommend that the lower bound of the confidence interval be equal to or no greater than one month. We continue to recommend that patients who are cancelled for the risk of ovarian hyperstimulation syndrome be considered treatment failures."

   - **Sponsor response: The sponsor does not concur with the Division's proposed "time-to-event" analysis. The sponsor states that time to clinical pregnancy is not on a "continuum," but dependent on the scheduling of an ultrasound to record clinical pregnancy status. Furthermore, the sponsor states that subjects may take a "break" in cycle treatment and this would artificially inflate the time to pregnancy.**

   Division's response to Serono's July 23, 2004 letter (item 2): The Division concurs with Serono that recognition of the precise time of clinical pregnancy is not on a continuum, neither is precise timing of a relapse/reoccurrence in a cancer study. We agree that time to clinical pregnancy requires a scheduled ultrasound visit just as documentation of relapse requires diagnostic medical documentation. We have recommended that ultrasound evaluation be scheduled at six weeks post-hCG in any cycle for which Luveris® is given and a positive serum hCG is obtained or at any subsequent time when biochemical pregnancy is noted when the subject is not using gonadotropin stimulation. Clinical pregnancy determination for the Luveris® plus r-hFSH arm and the r-hFSH arm would be handled in the same manner and all clinical pregnancies that result will be accounted for (data truncated at one year) as long as other gonadotropin drug products or assisted reproductive techniques are not used. Luveris® plus rhFSH should demonstrate superiority to rhFSH that is both statistically and clinically significant. The concern about "breaks" in cycle treatment should be negated by adequate randomization. The Division continues to recommend that cancelled cycles (to avoid the risk of ovarian hyperstimulation syndrome or any other reason) be considered as treatment failures.

3. July 8, 2004 Advice letter, item 8 – "We recommend that the inclusion criteria for estradiol be lowered to a serum estradiol level of < 20 pg/mL."

   - **The sponsor does not concur that the inclusion criteria of serum estradiol should be < 20 pg/mL, but states that it should be the same as previous studies of < 60 pg/mL.**

Division's response to Serono's July 23, 2004 letter (item 8): Serono references a single literature article from 1980 that stated that a serum estradiol of < 80 pg/mL was consistent with a negative progesterone challenge test.[2] Unfortunately the study was a retrospective examination of 89 patients with no evidence of estrogenic activity and low serum gonadotropin levels. The study started in 1963 and continued through 1979, and the authors acknowledge that serum gonadotropin levels were not available until 1977. The number of patients that actually had serum estradiol levels determined is unknown and the means and standard deviations seen in these patients are also unknown. Therefore, defining the serum estradiol level necessary to predict negative progesterone withdrawal bleeding (specifically for hypogonadotropic hypogonadal women) based on results published in this article is questionable. The Division, in considering Serono's discussion, also references one article from 1991 that suggested that endogenous estradiol levels were of limited predictive value in determining withdrawal bleeding.[3]

Therefore, we agree with Serono that there is no recognized standard diagnostic level of serum estradiol that identifies women with severe hypogonadotropic hypogonadism. Further, we acknowledge that serum estradiol is probably the least sensitive of the hormonal levels used in the clinical evaluation of these women. We propose that we discard use of estradiol levels (because of variability and lack of predictive value) and require, in addition to a negative progesterone challenge, two serum LH level determinations (obtained successively at least two weeks apart) less than 1.2 IU/L.[4]

[2] Schwartz M, Jewelewicz R, Dyrenfurth I, Tropper P, Van de Wiele R., "The use of human menopausal gonadotropins for the induction of ovulation. Sixteen years experience at the Sloane Hospital for Women." *Am J Ob Gyn* 1980; 138(7 pt 1): 801-7.

[3] Shangold MM, Tomai TP, Cook JD, Jacobs SL, Zinaman MJ, Chin SY, Simon JA., "Factors associated with withdrawal bleeding after administration of oral micronized progesterone in women with secondary amenorrhea." *Fertil Steril* 1991; 56(6):1040-7.

[4] Speroff L, Glass R, Kase N., *Clinical Gynecologic Endocrinology and Infertility.* Lippincott, Williams, and Wilkins. 1999; 429.

4. July 8, 2004 Advice letter, item 9 – "We do not agree with your definition of overall pregnancy rate. You have presented the definition of a biochemical pregnancy rate. We recommend defining overall pregnancy rate as the proportion of patients who demonstrate a doubling of serum β-hCG over 48-72 hours."

   - **The sponsor does not concur with the Division's definitions. The sponsor wishes a category called "overall pregnancy rate that includes clinical and biochemical pregnancy rates."**

   Division's response to Serono's July 23, 2004 letter (item 9): The **Centers for Disease Control and Prevention** (CDC) publish the current standard reporting terminology for reporting success rates in the United States.[5] In the most current (2001) edition, "success rates" were determined as follows:

1) Pregnancy – Reported as diagnosed using an ultrasound procedure.
2) Live Birth Rate - Birth of one or more living infants (delivery of multiple infants reported as one birth).
3) Singleton Birth Rate - Birth of a singleton liveborn infant.

The CDC report emphasizes live birth rate as the most clinically meaningful measure of success for patients. Pregnancy, live birth rates, and singleton livebirth rates were calculated based on the cycles started.

We strongly believe that reporting of success rates in labeling should be consistent with CDC recommendations. Our recommendation of "clinical pregnancy rate (defined as a pregnancy on ultrasound with a fetal heartbeat)"as the primary endpoint for the proposed study is a result of our recognition, at this time, of the additional burdens that requirements to determine live birth rates might impose on clinical trials.

[5]Centers for Disease Control and Prevention. 2001 *Assisted Technology Success Rates.* Palladian Partners Inc. December 6, 2003.

5. July 8, 2004 Advice letter, item 10 – We propose patients that have had their Luveris® dose titrated be excluded from this analysis.

   ➢ **The sponsor does not concur with the Division's recommendation and suggests that an additional analysis (with exclusion of any patient with a Luveris® dose titration) could be done.**

   Division's response to Serono's July 23, 2004 letter (item 10): We strongly believe that if investigators are allowed to titrate the dose of Luveris®, the results of the proposed Phase 4 trial will be uninterpretable. We recommend the use of a "modified" ITT population to exclude those subjects for whom the investigators allowed dose titration of Luveris® and to include only those subjects who remained on their specified fixed dose (75 IU and agreed upon lower dose) of Luveris®. If Serono seeks titration of Luveris® dosing for labeling purposes, then additional treatment arms could be proposed.

6. July 8, 2004 Advice letter, item 13 – "We do not concur with your hormonal criteria for follicular development, and you have not provided adequate literature support for your choice of cut-off values. The Division recommends more stringently defined (as supported by the literature) minimal (cut-off) levels for serum estradiol and progesterone levels (serum estradiol levels of $\geq$ 200 pg/mL and serum progesterone levels $\geq$ 10 ng/mL) to achieve successful follicular development."

   ➢ **The sponsor does not concur with the Division's suggested hormonal cut-offs and believes that the threshold values chosen were addressed during the Advisory Committee held September 30, 2003 and in the published literature. Serono also cites consistency with the Phase 3 trials.**

Division's response to Serono's July 23, 2004 letter (item 13): Our review of the September 30, 2003 Advisory Committee Meeting transcripts reveals no vote or consensus by the Committee on the levels of serum estradiol and serum progesterone that would define follicular development. Instead, individual committee members expressed an opinion. Drs. Giudice, Lewis and Keefe commented that the estradiol level used to determine follicular development in the previous studies appeared to be appropriate.

However, Dr. Liu, a recognized expert in the treatment of women with hypogonadotropic hypogonadism, stated regarding the appropriated estradiol level "I would disagree that 100 pg/mL is an appropriate marker. I think you are going to find the majority, in the normal menstrual cycle, it's about 300 – 350 pg/mL at the time of the LH surge, and that has been established by very sensitive RIA's (radio-immunoassays) and it is respectable."

The published literature submitted by Serono does not provide adequate documentation of the actual estradiol requirements in this hypogonadal hypogonadotropic population necessary to produce pregnancy, but rather remarks on the level of estradiol required to produce morphologic changes in the endometrium in normal and post-menopausal women. Morphologic changes in the endometrium are not the desired endpoint of patients, and may not be reflective of serum levels or pregnancy rates. Additionally, some of the submitted articles date back to the 1970's and 1980's and rely on hormonal assays that are no longer used.

Our recommendation for cut-off values for serum estradiol and serum progesterone levels is consistent with that offered as representative of those values obtained in a "normal" menstrual cycle in standard reproductive endocrinology textbooks and the published literature.[6,7,8]

Finally, Serono has previously represented that if the Division's recommended cut-off values for follicular development had been used in the Phase 3 trial, no change in outcome for success in follicular development would have resulted.

Our recommendation remains that the Phase 4 trials should incorporate a serum estradiol level of 200 pg/ml and a serum progesterone level of 10 ng/ml as criteria for adequate follicular development. Alternatively, Serono could submit or conduct a study using current hormonal assay standards to document the "standard" menstrual cycle hormonal values in a normal patient population.

[6]Speroff L, Glass R, Kase N. *Clinical Gynecologic Endocrinology and Infertility.* Lippincott, Williams, and Wilkins. 1999; 210.
[7]Martin K, Hall J, Adams J, Crowley W., "Comparison of exogenous gonadotropin and pulsatile gonadotropin-releasing hormone for induction of ovulation in hypogonadotropic amenorrhea." *J Clin Metab Endocrinol* 1993; 77(1): 125-9.
[8]Adams J, Taylor E, Schoenfeld D, Crowley W, Hall J., "The Midcycle Gonadotropin Surge in Normal Women Occurs in the Face of an Unchanging Gonadotropin-Releasing Hormone Pulse Frequency." *J Clin Metab Endocrinol* 1994; 79(3): 858-64.

If you have any questions, call Archana Reddy, M.P.H., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
8/26/04 01:10:27 PM
Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

7/8/04

NDA 21-322

INFORMATION REQUEST LETTER

Serono, Inc.
Attention: Pamela Williamson Joyce, RAC
Vice President, Regulatory Affairs and Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

Please refer to your April 30, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luveris® (lutropin alfa for injection).

Also, we refer to your May 25, 2004 submission, containing a complete response to our Not Approvable letter dated March 1, 2002.

We are currently reviewing the Clinical Section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA. Additional comments may follow.

1. Submit a revised safety update that includes information from Study 6905 as well as information from all other clinical studies, either completed or ongoing.

2. Confirm whether Luveris™ is now registered as a tradename (Luveris®).

If you have any questions, call Archana Reddy, M.P.H., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
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Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

7/8/04

NDA 21-322

Serono, Inc.
Attention: Pamela Williamson Joyce, RAC
Vice President, Regulatory Affairs and Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

Please refer to your April 30, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luveris® (lutropin alfa for injection).

Also, we refer to your May 25, 2004 submission, containing a complete response to our Not Approvable letter dated March 1, 2002.

We are reviewing your proposed labeling submitted on May 25, 2004. We request a prompt written response to the attached preliminary labeling comments in order to continue our evaluation of your NDA.

If you have any questions, call Archana Reddy, M.P.H., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

21 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

7/8/04

NDA 21-322

Serono, Inc.
Attention: Pamela Williamson Joyce, RAC
Vice President, Regulatory Affairs and Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

Please refer to your April 30, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luveris® (lutropin alfa for injection).

Also, we refer to your May 25, 2004 submission, containing a complete response to our Not Approvable letter dated March 1, 2002.

We are reviewing your proposed labeling submitted on July 23, 2004. We request a prompt written response to the attached preliminary labeling comments in order to continue our evaluation of your NDA.

If you have any questions, call Archana Reddy, M.P.H., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

19 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

7-8-04

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Margaret Kober
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Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

7/8/04

NDA 21-322

ADVICE LETTER

Serono, Inc.
Attention: Pamela Williamson Joyce, RAC
Vice President, Regulatory Affairs and Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

Please refer to your April 30, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luveris® (lutropin alfa for injection).

We also refer to your correspondence dated April 30, 2004, containing a proposal for a Phase 4 study to confirm the efficacy of Luveris®.

We have the following comments regarding your proposed Phase 4 study entitled, "A Phase 4 Clinical Trial to Confirm the Efficacy of the 75 IU Dose of Luveris® Versus Placebo when Co-Administered with Follitropin Alfa for Induction of Follicular Development and Pregnancy in Hypogonadotropic Hypogonadal Women with Profound LH Deficiency, as Defined by a Baseline LH Level < 1.2 IU/L." We request a prompt written response in order to continue our evaluation of your NDA. Additional comments may follow.

1. We recommend that your proposed Phase 4 study be designed to identify the lowest effective dose and that you evaluate a dose of Luveris® lower than 75 IU as well as the 75 IU dose.

2. We recommend that the primary efficacy analysis be an intent-to-treat analysis of time from randomization to the occurrence of a clinical pregnancy, recognized as a gestational sac with fetal heart motion on vaginal ultrasound at six weeks post-embryo transfer. We recommend a two-sided 95% or one-sided 97.5% confidence interval analysis of the difference. To demonstrate efficacy, we recommend that the lower bound of the confidence interval be equal to or no greater than one month. We continue to recommend that patients who are cancelled for the risk of ovarian hyperstimulation syndrome (OHSS) be considered treatment failures.

3. We recommend that per cycle clinical pregnancy rate analyses and cumulative cycle analyses be considered secondary analyses.

4. We recommend that the specific clinical diagnosis of each patient entering the trial be recorded in detail, rather than categorizing as primary or secondary amenorrhea.

5. We recommend that you record in detail the results of the baseline semen analysis (number of total sperm and percentage motile sperm).

6. We recommend that you modify the entry criteria to increase the age for inclusion to 40 years of age.

7. We recommend excluding patients undergoing *in-vitro* fertilization, intracytoplasmic injection, or any other concomitant Assisted Reproductive Technology procedure other than intrauterine insemination.

8. We recommend that the inclusion criteria for estradiol be lowered to a serum estradiol level less than 20 pg/mL.

9. We do not agree with your definition of overall pregnancy rate. You have presented the definition of a biochemical pregnancy rate. We recommend defining overall pregnancy rate as the proportion of patients who demonstrate a doubling of serum β-hCG over a 48 to 72 hour time period.

10. We propose patients that have had their Luveris® dose titrated be excluded from the primary efficacy analysis.

11. We recommend a classification of severe for any OHSS patient that is hospitalized or requires aggressive treatment (such as albumin or paracentesis).

12. We recommend inclusion of the following secondary efficacy endpoints:
    a. Mean estradiol values on the day of human chorionic gonadotropin (hCG) administration.
    b. Cycle cancellation rate.
    c. Livebirth rate.
    d. Total vials of gonadotropin used per cycle.
    e. Total duration of gonadotropin use.
    f. Rate of spontaneous abortion.
    g. Rate of ectopic pregnancy.

13. We do not concur with your hormonal criteria for follicular development, and you have not provided adequate literature to support your choice of cut-off values. We recommend more stringently defined (as supported by the literature) minimal cut-off levels for serum estradiol and progesterone levels (serum estradiol levels of $\geq$ 200 pg/mL and serum progesterone levels $\geq$ 10 ng/mL) to achieve successful follicular development.

14. We recognize that measuring endometrial thickness is a research tool; however, we recommend that endometrial thickness be assessed as a secondary efficacy endpoint.

15. We recommend that you include the following additional safety endpoints:
    a. Incidence of multi-fetal gestation.
    b. Incidence of fetal anomalies.
    c. Incidence of second and third trimester fetal loss.
    d. Incidence of birth defects.

If you have any questions, call Archana Reddy, M.P.H., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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Margaret Kober
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Chief, Project Management Staff

NDA: 21-322
Drug: Luveris® (lutropin alfa for injection)
Sponsor: Serono, Inc.

User Fee Goal Dates

The user fee goal date for this new drug application is November 26, 2004.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

6/10/04

NDA 21-322

Serono, Inc.
Attention: Pamela Williamson Joyce, RAC
Vice President, Regulatory Affairs and Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

We acknowledge receipt on May 26, 2004, of your May 25, 2004, resubmission to your new drug application for Luveris® (lutropin alfa for injection).

We consider this a complete, class 2 response to our Not Approvable action letter dated March 1, 2002. Therefore, the user fee goal date is November 26, 2004.

If you have any questions, call Archana Reddy, M.P.H., Regulatory Project Manager, at (301) 827 - 4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
6/10/04 01:15:08 PM
for Margaret Kober

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

5/24/04

NDA 21-322

Serono, Inc.
Attention: Pamela Williamson Joyce, R.A.C.
Vice President, Regulatory Affairs and Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

Please refer to your new drug application (NDA) dated April 30, 2001, received May 1, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luveris™ (lutropin alfa for injection).

We also refer to your correspondence dated April 30, 2004, containing a proposal for a phase 4 study to confirm the efficacy of Luveris™.

We have reviewed your submission and have the following comments. Additional clinical and statistical comments may be generated upon review of the full study protocol when submitted.

1. The Division has concerns about drop-outs since cumulative cycles will be used in calculating clinical pregnancy rates. If cumulative cycles are to be evaluated, then drop-outs due to lack of efficacy and ovarian hyperstimulation may cause an imbalance between treatment arms. Therefore, we recommend you consider an appropriate drop-out rate in calculating the number of patients needed in both treatment arms.

2. We recommend that you obtain detailed historical information on the medical diagnosis responsible for the amenorrhea in each subject enrolled (in addition to documenting whether the patient had primary or secondary amenorrhea). In this manner, patients with disorders such as Kallman's and panhypopituiarism can be evaluated.

3. We recommend that patients entering this study be gonadotropin-naïve.

4. Although follicular development and ovulation are not primary endpoints, both efficacy endpoints should use a more stringent cut-off of 10 ng/mL of serum progesterone instead of the proposed 7.9 ng/mL cut off.

5. We recommend that a proposed 200 pg/mL level is a more acceptable estradiol level as an indicator of follicular development than the proposed 109 pg/mL level.

6. We recommend that biochemical (overall) pregnancy rates be determined by rising serum β-hCG levels.

7. We recommend that patients who undergo adjunct ART procedures including: in vitro fertilization (IVF), intracytoplasmic injection (ICSI), Gamete Intrafallopian Transfer (GIFT) and Zygote Intrafallopian Transfer (ZIFT) be excluded.

8. We recommend that patients who are cancelled for a risk of ovarian hyperstimulation syndrome be counted as failures, not as successes.

9. We recommend standardization of luteal phase treatment protocols.

10. We recommend that you record final pregnancy outcomes (livebirth, miscarriage, ectopic).

If you have any questions, call Archana Reddy, M.P.H., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
5/24/04 07:46:55 PM
Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-322

4/30/04

Serono, Inc.
Attention: Pamela Williamson Joyce
Vice President, Regulatory Affairs
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

Please refer to your new drug application (NDA) dated April 30, 2001, received May 1, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luveris® (lutropin alfa for injection).

We also refer to the March 1, 2002, letter which stated that NDA 21-322 was not approvable because the submitted data did not provide sufficient evidence to support the efficacy of Luveris® 75 IU/day in follicular development and ovulation induction in hypogonadotropic hypogonadal women with profound LH deficiency (LH < 1.2 IU/L) and infertility. At subsequent meetings held on May 10, 2002, and January 9, 2003, we discussed options for addressing the deficiency identified in that letter, and reiterated our request for an additional pre-approval placebo-controlled dose-ranging study with ovulation induction as the primary efficacy endpoint. On April 28, 2003, we received preliminary information on Study 21415, an open-label extension to the previously submitted Study 21008. In addition, the agency held a meeting of the Reproductive Health Drugs Advisory Committee on September 30, 2003, to seek expert advice regarding the selection, definition, and analysis of the efficacy endpoints in your studies. We also refer to your written response dated January 30, 2004, addressing questions raised by the division at our January 9, 2004, meeting.

We have carefully considered the recommendations from the Advisory Committee and discussion points raised by your firm and have concluded that induction of follicular development is an acceptable efficacy endpoint for clinical trials conducted in infertile, profoundly LH-deficient women with hypogonadotropic hypogonadism. We have also concluded that the results from Studies 21008 and 6253 demonstrate that Luveris® 75 IU, when administered concomitantly with FSH, induces follicular development in this population of infertile women. These studies however, do not demonstrate a positive effect on clinical pregnancy rate. Study 21415 evaluated titratable FSH dosing with the dose of Luveris® fixed at 75 IU and demonstrated a 36% clinical pregnancy rate after one cycle. While reassuring, this finding is not definitive because there was no placebo comparator group in Study 21415, and the finding has not been replicated in a second trial.

We believe that infertility in the context of hypogonadotropic hypogonadism and profound LH deficiency defined above is a serious condition with very limited options for pregnancy. Therefore, we have determined that NDA 21-322 may be considered under the accelerated approval regulations, Subpart H, 21 CFR 314.510, acknowledging that induction of follicular

development is a surrogate endpoint that is reasonably likely to predict the clinical benefit of pregnancy in infertile, profoundly LH-deficient women with hypogonadotropic hypogonadism. Approval of NDA 21-322 under 21 CFR 314.510 would be subject to the requirement that you conduct an adequate and well-controlled postmarketing study to verify and describe the clinical benefit of Luveris® with respect to pregnancy. Furthermore, under 21 CFR 314.530, FDA may withdraw marketing approval for Luveris® if a postmarketing study fails to verify clinical benefit or if you fail to perform the required postmarketing study with due diligence.

If you wish to pursue approval under Subpart H, we will accept the following components as a complete response to the Not Approvable letter of March 1, 2002. The request in the Not Approvable letter to conduct a pre-approval placebo-controlled, dose-ranging study to evaluate ovulation induction in hypogonadotropic hypogonadal women with profound LH deficiency and infertility is not necessary for approval under Subpart H as described above. Previously submitted information may be incorporated by reference into your complete response. Before your application may be approved, you will need to submit the following:

1. The final study report for Study 21415;

2. Your proposed protocol, to confirm clinical benefit, for a randomized, double-blind, placebo-controlled postmarketing study with pregnancy as the primary endpoint in profoundly LH-deficient infertile women with hypogonadotropic hypogonadism when Luveris® is concomitantly administered with titratable FSH. Prior to approval, agreement must be reached on the overall study design and analysis plan, as well as your proposed times for initiation of patient enrollment, completion of enrollment, and submission of the final study report to the division;

3. Draft professional labeling that:

- Specifies in the INDICATIONS AND USAGE section that Luveris®, administered with follitropin alfa for injection, is indicated for induction of follicular development in hypogonadotropic hypogonadal infertile women with severe LH (< 1.2 IU/L) deficiency, and that a definitive effect on pregnancy in this population has not been demonstrated; and

- Includes a description of the design and major findings of Studies 21008 and 6253 in the CLINICAL STUDIES subsection of the CLINICAL PHARMACOLOGY section; for each study, the results of the analysis of the composite primary efficacy endpoint of follicular development (follicle size, pre-ovulatory estradiol level, and mid-luteal phase P_4 level) should be presented (a) with cycle cancellation for the risk of ovarian hyperstimulation syndrome (OHSS) counted as a success, and (b) with cycle cancellation for the risk of OHSS counted as a failed response; and

4. A safety update as described in the Not Approvable letter dated March 1, 2002, and required under 21 CFR 314.50(d)(5)(vi)(b), including data from preclinical and clinical studies and a summary of the worldwide safety experience with the drug.

Note that these are recommended components of a complete response. Additional information requests and potential review issues may arise as we proceed in our review of the complete response submission.

The drug product may not be legally marketed until you have been notified in writing that the application has been approved.

If you have any questions, please call Archana Reddy, M.P.H., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
4/30/04 09:24:34 AM

Food and Drug Administration
Center for Drug Evaluation and Research

Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: February 6, 2004

To: Pamela Williamson Joyce, Vice President Regulatory Affairs Cc: Lisa Mills Manager, Regulatory Affairs	**From:** Archana Reddy, M.P.H. Regulatory Project Manager
Company: Serono, Inc.	Division of Division of Reproductive and Urologic Drug Products
Fax number: 781-681-2924	**Fax number:** 301-827-4260
Phone number: 781-681-2273	**Phone number:** 301-827-4260

Subject: Meeting minutes of January 9, 2004 meeting for NDA 21-322 (Luveris)

Total no. of pages including cover: 5

Comments:

Pamela,

Please find attached the meeting minutes from the 1/09/04 meeting for Luveris.

Archana Reddy

Document to be mailed: ☐ YES ☑ NO

MEETING MINUTES

Date: January 9, 2004 **Time:** 11:00 A.M. – 12:00 P.M.

Location: Parklawn Building, Chesapeake Conference Room

NDA Number: 21-322 **Drug:** Luveris™ (lutropin alfa for injection)

Indication: Stimulation of follicular development and ovulation in infertile women with severe deficiency in LH

Sponsor: Serono, Inc.

Type of Meeting: Type A (Stalled Programs)

Meeting Chair: Daniel Shames, M.D.

External Participant Lead: Pamela Williamson Joyce

Meeting Recorder: Archana Reddy, M.P.H.

FDA Attendees:
Daniel Shames, M.D., Director, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
Shelley Slaughter, M.D., Ph.D., Medical Team Leader, DRUDP (HFD-580)
Scott Monroe, M.D., Medical Team Leader, DRUDP (HFD-580)
Audrey Gassman, M.D., Medical Officer, DRUDP (HFD-580)
Archana Reddy, M.P.H., Regulatory Project Manager, DRUDP (HFD-580)
Margaret Kober, R.Ph., Chief, Project Management Staff, DRUDP (HFD-580)
Kate Meaker, M.S., Division of Biometrics II (DB II) @ DRUDP (HFD-580)

External Participants
Serono, Inc.
Pamela Williamson Joyce, Vice President, US Regulatory Affairs
Lisa S. Mills, Manager, Regulatory Affairs
Paul Lammers, M.D., Acting Director of Reproductive Health
Susan Kenley, Ph.D., Worldwide Director, Biometrics

Consultant
[ ]

Background:
NDA 21-322 (Luveris™) received a Not Approvable (NA) action letter on March 1, 2002. The sponsor requested a Type A meeting on April 3, 2002, to discuss the NA letter, the

request for an additional Phase 3 study, and the options for addressing the Agency's concerns. A Type A meeting was held on May 10, 2002. An advisory committee meeting to discuss this NDA application in particular was held on September 30, 2003. On December 11, 2003, the sponsor requested another Type A meeting to discuss resolution of the deficiencies identified in the March 1, 2002 Not Approvable (NA) action letter issued by the Agency and the results of the Advisory Committee meeting as it relates to their Luveris ™ application. The Type A meeting package was received on December 11, 2003.

Meeting Objective:
To continue discussion of the not approvable action for Luveris™, the committee opinion from the September 30, 2003 Advisory Committee Meeting, and possible resolution of the deficiencies as identified in the March 1, 2002 Not Approvable letter.

Discussion:
The meeting commenced with a general overview by the Division Director. In this overview, the Division Director:

- reiterated that his review of the history of drug development showed that the Division had recommended to the Sponsor on multiple occasions that ovulation rate be the primary efficacy variable and the clinical review team strongly considered efficacy for ovulation rate as well as the review team's determination of efficacy for follicular development.
- restated that he felt communications on the part of the Division and the Sponsor could have been better
- stated the Division's view that the Advisory Committee's recommendations were mixed; advising that the drug product had not demonstrated efficacy for ovulation induction but had demonstrated efficacy for follicular development by the Sponsor' definition of follicular development

The Sponsor:

- pointed out that the follicular development endpoint did include the Division's recommended use of P4 (progesterone levels)
- held that the Advisory Committee's *recommendation* was that follicular development should be used for WHO Type I anovulatory patients and that the committee had recommended that efficacy was demonstrated in Study 21008 for this population of women

The Division Director:

- invited Serono to send in any portions of the Advisory Committee transcript that they feel supports their contentions
- [redacted]

submitted to IND 44,108

The Sponsor:

- agreed to send in to the Division any portions of the transcript that support their contentions
- [illegible]

Action Items:

- The sponsor will send references made to the transcripts of the Advisory Committee meeting held on September 29 and 30, 2003 to the Division.
- The sponsor will send the meeting minutes of the meeting held in 1999 where there was discussion of P4 combined as the endpoint.
- The Division Director will review this application, the regulatory and scientific history and the Advisory Committee Transcripts and make his decision regarding approvability.
- If the decision on the final action does not change, then the Sponsor has a right to appeal this decision to the Office Level. The Sponsor indicated that they would appeal if there was not a change in status of the application.

Signature: Meeting Chair
See appended electronic signature page
Daniel Shames, M.D.

Note to Sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

Cc:
Arch NDA
HFD-580/Division Files
HFD-580/Reddy/Shames/Slaughter/Monroe/Gassman/Meaker/Kober

Created by: Archana Reddy, January 12, 2004
Concurrence: km/, January 21, 2004, ag/January 20, 2004, mk/February 2, 2004, srs/February 6, 2004, das/February 6, 2004
Finalized: Archana Reddy, February 6, 2004

Meeting Minutes

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/s/

Daniel A. Shames
2/6/04 03:22:32 PM

MEETING MINUTES

Date: January 9, 2003 **Time:** 1:00 – 2:30 A.M. **Location:** Conf. Rm I

NDA Number: 21-322 **Drug:** Luveris™ (lutropin alfa for injection)

Indication: Stimulation of follicular development and ovulation in infertile women with severe deficiency in LH

Sponsor: Serono, Inc.

Type of Meeting: Type A (End-of-Review)

Meeting Chair: Shelley Slaughter, M.D., Ph.D.

External Participant Lead: Pamela Williamson Joyce

Meeting Recorder: Archana Reddy, M.P.H.

FDA Attendees:
Daniel Shames, M.D., Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
Donna Griebel, M.D., Deputy Director, DRUDP (HFD-580)
Shelley Slaughter, M.D., Ph.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products (HFD-580)
Audrey Gassman, M.D., Medical Officer, DRUDP (HFD-580)
Archana Reddy, M.P.H., Project Manager, DRUDP (HFD-580)
Kate Meaker, M.S., Division of Biometrics II (DB II) @ DRUDP (HFD-580)

External Participants
Serono, Inc.
Aliza Eshkol, Ph.D., Senior Scientific Advisor, Corporate Research and Development
Pamela Williamson Joyce, Vice President, US Regulatory Affairs
Lisa S. Mills, Manager, Regulatory Affairs
Thomas Lang, Vice Chairman and Senior Policy Advisor
Paola Ricci, Senior Executive Vice President, Worldwide Regulatory Affairs
Fanny O'Brien, Ph.D., Manager, Biometrics
Paul Lammers, M.D., Acting Director of Reproductive Health
Susan Kenley, Ph.D., Worldwide Director, Biometrics
[ ] Consultant

Background:
NDA 21-322 (Luveris™) received a not approvable (NA) action letter on March 1, 2002. The sponsor requested a Type A meeting on April 3, 2002, to discuss the NA letter, the request for an additional Phase 3 study, and the options for addressing the Agency's concerns. A Type A meeting was held on May 10, 2002. The sponsor has requested

another meeting to discuss resolution of the deficiencies identified in the March 1, 2002 not approvable (NA) action letter issued by the Agency. The Type A meeting package was received on December 4, 2002.

Meeting Objective:
To continue discussion of the not approvable action for Luveris™ and resolution of the deficiencies as identified in the March 1, 2002 NA letter.

Discussion:

- Study 21008
  - According to Serono the primary endpoint was a composite endpoint with three criteria (follicle size, attainment of a specified serum estrogen level and attainment of a specified progesterone level indicating ovulation)
  - Serono referenced the May 1999 meeting minutes in which the Division agreed to the combination endpoint; Division referenced the February 23, 1999 meeting minutes in which the Division specified that the primary endpoint should be ovulation with pregnancy as the secondary endpoint;
- Serono rejected the Division's recommendation holding that the use of ovulation rates as the primary endpoint would be burdensome due to the risk of cycle cancellation due to the risk of OHSS; this became a review issue
- At the December 2000 Pre-NDA meeting with Serono, the Division did not discuss concerns over trial and the endpoints evaluated with the sponsor; there was no clinical comment according to the sponsor
- DRUDP emphasized that the Division does not discuss the outcome of review at the Pre-NDA meeting
- Dr. Shames acknowledged that there is scientific disagreement on endpoints, data analyses and interpretation; with respect to communication Dr. Shames stated that, the Division could have been clearer but the sponsor also did not always take into account the Division's advice during drug development of Luveris
- the Division clinical and statistical reviewers have determined that there is insufficient data to support efficacy of the drug product; Luveris™ (LH)and Gonal-F® (FSH) combination did not beat Gonal-F® alone (placebo for LH)
- at a minimum, , the patients and physicians should have assurances that Luveris is better than Gonal-F alone; there was not a single positive study presented by Serono
- the Division made Serono aware that it would be evaluating the surrogate endpoint of ovulation rates to assess efficacy; but ultimately would rather that a surrogate endpoint not be used and clinical pregnancy rate be evaluated as the primary endpoint
- Study 21008 and Study 6253 do not establish that there is a difference in ovulation rate between Luveris™ plus Gonal-F® vs Gonal-F® alone
- When subjects removed for the risk of ovarian hyperstimulation syndrome (OHSS) are not counted as successes then the difference in outcome of the analyses for efficacy by the Division vs. that of Serono rest upon one subject in Study 21008, the

small pivotal trial; this subject did not meet the serum estradiol criterion for follicular development (development); Study 6253 does not have positive results when subjects removed for the risk of OHSS are not counted as successes

- Study 6905 (U.S. Study) failed to show efficacy in the more broadly -defined population of hypogonadotropic hypogonadal subjects, but in the more narrowly-defined population (i.e. LH< 1.2), the analysis suggested that 25 I.U. may not be different from the 75 I.U. dose; however the numbers were too small to make any efficacy conclusions
- Serono indicated that in Study 6905, women were not shown to be functionally hypoestrogenic, i.e this study did not have an enrollment requirement to demonstrate a negative progesterone challenge; 24 hour urine collections would have been ideal; but not practical
- the Division maintains that the 75 I.U. dose has not been shown to demonstrate efficacy, however, the studies may not have been sufficiently powered to demonstrate efficacy; the Division is convinced that the Sponsor should also evaluate doses lower than 75 I.U.(i.e lower doses than the 75 IU dose may be shown to have efficacy in the appropriately designed and powered study)
- Serono reiterated that it felt that the 75 I.U. dose is efficacious and has better overall profile with respect to serum estrogen production than lower doses; Serono maintained that too many patients would be needed to show the difference between the 75 I.U. dose and lower doses
- the Division appreciates that the patient population is rare but feels that sufficient subjects could be recruited to look at a 75 I.U dose and at least one lower dose as well as placebo

Decisions Reached:

- DRUDP presented Serono with three different options for addressing the NA action for Luveris:
  - Serono can appeal the Not Approvable action to the ODE III immediate Office if they choose to.
  - An advisory committee meeting will be held over a two-day period in approximately 6 months to discuss assisted reproductive technology products in general and the not approvable action issued for Luveris.
  - The sponsor can file an amendment to their NDA addressing the deficiencies as outlined in the not approvable action letter; specifically conduct another Phase 3 trial.

Action Items:

1) The PM will fax the meeting minutes to the sponsor within 30 days.
2) The sponsor will submit Study 21415 officially to the NDA for review by DRUDP.

_____
Signature, Meeting Chair
See appended electronic page

Note to Sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcome.

Cc:
Arch NDA
HFD-580/Division Files
HFD-580/Reddy/Kober/Meaker/Slaughter/Shames/Griebel

Created by: Archana Reddy, February 3, 2003
Concurrence: km/February 3, 2003, ag/February 10, 2003, ss/February 7, 2003, das/February 10, 2003
Finalized: ar/February 10, 2003
Filename/Path: C:Data/My Documents/NDAs/N21322/1-09-03minutes.doc

Meeting Minutes

5 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

12-24-01

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/s/

Shelley Slaughter
2/10/03 04:34:34 PM
I concur.

MEETING MINUTES

Date: May 10, 2002 **Time:** 10:00 – 11:30 A.M. **Location:** Conference Room B

NDA Number: 21-322 **Drug:** Luveris™ (lutropin alfa for injection)

Indication: Stimulation of follicular development and ovulation in infertile women with severe deficiency in LH

Sponsor: Serono, Inc.

Type of Meeting: Type A (End-of-Review)

Meeting Chair: Shelley Slaughter, M.D., Ph.D.

External Participant Lead: Steve Knezevic, M.D., Ph.D.

Meeting Recorder: Archana Reddy, M.P.H.

FDA Attendees:
Shelley Slaughter, M.D., Ph.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products (HFD-580)
Ridgely Bennett, M.D., Medical Officer, DRUDP (HFD-580)
Archana Reddy, M.P.H., Project Manager, DRUDP (HFD-580)
Margaret Kober, R.Ph., Chief, Project Management Staff, DRUDP (HFD-580)
Kate Meaker, M.S., Division of Biometrics II (DB II) @ DRUDP (HFD-580)

External Participants
Serono, Inc.
Aliza Eshkol, Ph.D., Senior Scientific Advisor, Corporate Research and Development
Pamela Williamson Joyce, Vice President, US Regulatory Affairs
Thomas Lang, Vice Chairman and Senior Policy Advisor
Paola Ricci, Senior Executive Vice President, Worldwide Regulatory Affairs
Steve Knezevic, M.D., Ph.D., Senior Vice President, Clinical Development
Fanny O'Brien, Ph.D., Manager, Biometrics

Consultant
[redacted]

Background:
NDA 21-322 (Luveris™) received a not approvable (NA) action letter on March 1, 2002. The sponsor requested a Type A meeting on April 3, 2002, to discuss the NA letter, the request for an additional Phase 3 study, and the options for addressing the Agency's concerns.

Meeting Objective:

To discuss the not approvable action for Luveris™.

Discussion:
The sponsor did not expect to receive a not approvable action for Luveris™ based upon the Pre-NDA meeting that was held for this drug product.

Clinical

- LH supplementation of FSH is a long-established therapeutic modality in the treatment of hypogonadotropic hypogonadism (H.H.)
- the original labeling submitted by the sponsor was for ovulation induction in infertile women with severe LH deficiency; menotropins have been used for this purpose "off label", but menotropins were never evaluated by the FDA for this indication and it is difficult to determine if menotropins are effective for this indication.
- overall, it is difficult to determine if this drug has any or much benefit for this indication; the original U.S. study (Study 6905), conducted in a traditional population of H.H. as determined by Serono's expert clinical investigators, yielded results that indicated that Luveris is ineffective for treatment of H.H.
- while it is known that menotropins have been used, off label, for the treatment of H.H. for many years, there is no good data to show how effective it is
- considerable variation exists in the endocrine profile of H.H.; there is some overlap in hormone levels between H.H. subjects and normal women and randomly obtained serum gonadotropin levels may be low or normal
- it is known that some H.H. patients respond to FSH alone
- Shoham, in 1991, compared treatment of profoundly deficit H.H. patients using menotropins in one cycle of treatment, and FSH alone in the next cycle of treatment; all patients had screening LH of $\leq$ 1.2 IU/L; when menotropins were given, all 9 patients ovulated as determined by luteal phase serum progesterone levels; when FSH alone was administered, three of the subjects ovulated, indicating that LH was not required
- there was nothing in the endocrine characteristics of those responding to FSH alone that differentiated them from non-responders or that would have predicted a response; clearly, some profoundly LH-deficient patients respond to FSH alone
- in women undergoing gonadotropin therapy, an excessive response to follicular stimulation may lead to the development of OHSS, a life-threatening condition, particularly if hCG is given to induce ovulation
- subjects in Serono's studies were considered at risk of developing OHSS if serum estradiol concentrations increased rapidly and/or there was an excessive number of growing follicles visualized; in such cycles, hCG was to be withheld and the cycle cancelled; risk of OHSS is a safety-related event and was to be recorded as such
- in Study 6905 and Study 6253, trend analyses were performed with and without overstimulation counted as a success

- in Study 21008, overstimulation resulting in cancellation of the cycle was considered a success; the sponsor questioned whether cancelled cycles due to overstimuation should be counted as successes or failures; from a clinical standpoint, for the treating physician and the patient, they are failures
- cycle cancellation due to risk of OHSS is not a benefit for the patient and not a success for the patients
- Serono acknowledged the above point in their supplemental pre-meeting package dated November 18, 1998; in the discussion of the ITT analysis of study 6253, the sponsor stated that follicular development occurred in 70.0 % of patients receiving 225 IU of Luveris™ and in 63.6 % of patients receiving 75 IU of Luveris™
- the 6.4 % increased response seen in the 225 IU group (70.0 % versus 63.6 % in 75 IU) was associated with a greater likelihood of cycle cancellation due to risk of OHSS; for the 6.4 % gain in efficacy at this higher dose, there was an approximately 12 % increase in cycle cancellation due to risk of hyperstimulation; for this reason, 225 IU was not chosen as the appropriate dose and 75 IU was chosen by the sponsor as the appropriate dose
- in study 21008, there was a 27 % gain in efficacy claimed by counting 23 % of patients with cancelled cycles as successes; Serono was informed in a teleconference February 23, 1999, that a decision had been made that the primary clinical endpoint should be ovulation rates with pregnancy rates as a secondary outcome; ovulation would be determined on the basis of mid-luteal phase serum progesterone levels
- on this basis, success occurred in only 46 % of patients receiving 75 IU of Luveris™
- if the patients with cancelled cycles receiving 75 IU of Luveris™ had been given 25 IU or 50 IU of Luveris™ and ovarian hyperstimulation had not occurred, a much larger percentage of patients would have benefited by successful ovulation
- on the basis of all currently available data, one cannot determine that the benefit to risk ratio for this drug is favorable; ovulation occurred in 45 % of patients receiving 75 IU of Luveris™ in study 6253
- DRUDP informed the sponsor, during the February 23, 1999 teleconference, that the lowest effective dose for Luveris had not been clearly established; Serono's response to DRUDP's strong recommendation to use ovulation rates as the primary efficacy endpoint is dated March 22, 1999; Serono indicated that primary endpoint would be follicular development and that it would be burdensome to use ovulation rates as the primary endpoint since some patients will be cancelled for risk of OHSS and will not reach ovulation
- Serono submitted a final protocol dated June 15, 1999, which included a discussion of Study 6253; the results of the analysis of the primary endpoint, follicular development, for the ITT population is presented; the same is true for Study 6905
- as stated by Serono, the progesterone assessment does address ovulation and ovulation is what DRUDP analyzed
- there is not sufficient evidence to show that Luveris 75 IU treatment group is not statistically significantly different than the placebo group

- DRUDP's intent-to-treat analysis of "follicular development" Luveris is not statistically significantly different from the placebo group
- Serono's analysis of follicular development on which the claim of efficacy is based is not scientifically valid in that failures were counted as successes; i.e., patients cancelled for risk of OHSS were counted as successes
- no data to show effectiveness of the 75 I.U. dose; no LH product alone approved for anything; only combination of LH and FSH used
- according to Serono, this drug product has been on the market in the European Union for a year and three months and no adverse events have been reported (both serious and non-serious)
- Per Serono, a total of 1300 patients who met entry criteria of LH< 1.2 received this treatment; some of the patients were in clinical trials but it is not clear if all the patients met the entry criteria
- in the past, DRUDP emphasized to sponsor that the problem is efficacy not safety, reasonable criteria for risk of OHSS and lower cancellation rates should be established
- Serono can merge the two studies (Study 6253 and Study 21008); but the results would only be considered supporting data; DRUDP recommends that a new Phase 3 clinical trial be conducted
- Serono indicated to DRUDP that Study 21008 extension (up to 3 additional cycles with the 75 IU dose of Luveris) is still being analyzed; DRUDP emphasized that this would not address the primary efficacy issue
- DRUDP indicated to Serono that the approval of currently approved drug products for ovulation induction was based on the efficacy during the first cycle of treatment
- originally 2 identical protocols (one in U.S. and one in Europe to give enough power) were proposed by Serono to support the approval of the drug product; subsequently it was agreed that positive evidence from a single Phase 3 clinical trial would be accepted as sufficient
- DRUDP clarified for Serono the basis of the not approvable action
- to address the clinical deficiency, DRUDP requires a randomized, double-blind, placebo controlled study using ovulation rates as the primary endpoint
- DRUDP recommended to Serono that they study one or two lower doses in addition to the 75 IU dose
- any additional data would be considered supportive

Statistical

- in study 6905, the sponsor intended to consider patients with the risk of OHSS as successes; risk of OHSS as a success or failure was not discussed with the Agency according to the sponsor

- DRUDP gave a strong recommendation to evaluate ovulation rates; population and dose was discussed; sponsor did not follow these recommendations; thus, this issue became a review issues
- Serono proposed submitting the extension data on ovulation rates and pregnancy; post-hoc analysis proposed would not be sufficient to address the efficacy question; sponsor will provide follow-up data for the 75 I.U. group; additional cycles to be submitted for review are not nascent cycles; DRUDP indicated that this is unacceptable as the sponsor agreed with the requirement to demonstrate that the drug is more effective than placebo
- Serono proposed to combine the study populations for Study 6253 and Study 21008; DRUDP noted the two Phase 2 trials had different patient populations; the single Phase 3 trial (Study 21008) alone could not beat placebo; Serono should pursue further evidence, not just reshuffle and present existing evidence
- Serono raised the point that the protocol included that the risk of OHSS was to be counted as a success in evaluating "follicular development"; DRUDP indicated that it had strongly recommended that ovulation rate not follicular development be the primary endpoint

Decisions Reached:

- Serono can appeal the Not Approvable action to the ODE III immediate Office if they choose to
- Serono should submit for review to DRUDP a protocol for a new trial looking at ovulation rates to support efficacy; Serono should propose the dose or doses to be evaluated; DRUDP recommends that Serono include for study one or two doses lower than the 75 IU dose as well as the 75 IU dose

Action Items:

1) The PM will fax the meeting minutes to the sponsor within 30 days.

_____
Signature, Meeting Chair
See appended electronic page

Note to Sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcome.

Cc:
Arch NDA
HFD-580/Division Files
HFD-580/Reddy/Kober/Bennett/Meaker/Slaughter/Shames

Created by: Archana Reddy, May 28, 2002
Concurrence: rb/May 31, 2002, km/June 5, 2002, mk/June 5, 2002, ss/June 7, 2002
Finalized: ar/June 10, 2002
Filename/Path: C:Data/My Documents/NDAs/N21322/naminutes.doc

Meeting Minutes

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/s/

Shelley Slaughter
6/10/02 11:52:26 AM
I concur.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: March 1, 2002

To: Pamela Williamson Joyce Vice President, Regulatory Affairs Cc: Lisa Mills, Manager, Regulatory Affairs	**From:** Archana Reddy, M.P.H. Regulatory Project Manager
Company: Serono, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 781-681-2947	**Fax number:** 301-827-4267
Phone number: 781-681-2273	**Phone number:** 301-827-4260

Subject: Courtesy fax for NDA 21-322 (action letter)

Total no. of pages including cover: 6

Comments:

Pamela,

Attached is the action letter for Luveris™.

Archana Reddy

Project Manager/DRUDP

Document to be mailed: ☐ YES ☑ NO

MEMORANDUM OF TELECON

DATE: February 28, 2002

APPLICATION NUMBER: NDA 21-322, Luveris™ (lutropin alfa for injection)

BETWEEN:

Name: Pamela Williamson Joyce, Vice President, Regulatory Affairs
Phone: (781) 681 - 2298
Representing: Serono, Inc.

AND Name: Daniel Shames, M.D., Acting Division Director
Archana Reddy, M.P.H., Project Manager
Diane Moore, Regulatory Project Manager
Margaret Kober, Acting Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: To convey the not approvable action to the sponsor for NDA 21-322 (Luveris™).

DISCUSSION:
The Division informed the sponsor that they would be receiving a not approvable action letter for Luveris™. The sponsor was given the following options:

1) Withdraw the NDA before noon on March 1, 2002.
2) Request a Type A meeting to discuss the not approvable action.
3) Appeal the action to the ODE III immediate office.
4) File an amendment to the NDA.

Decision Reached:
The sponsor will consider their options and inform the Division of their decision.

Action Item:
1) The PM will fax the minutes of the teleconference to the sponsor within 30 days.

Post-Meeting Addendum:
The sponsor indicated on March 8, 2002, via fax, that they intend to file an amendment to the NDA.

/S/

Daniel Shames, M.D.
Acting Division Director

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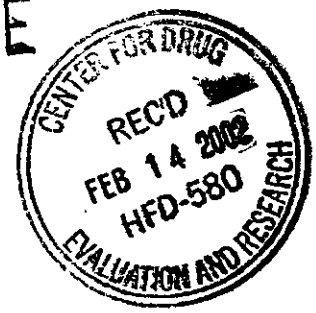
/s/

Archana Reddy
3/18/02 01:19:43 PM
CSO

Daniel A. Shames
3/18/02 05:52:52 PM
MEDICAL OFFICER

CONFIDENTIAL

DUPLICATE



Serono, Inc.
One Technology Place
Rockland, MA 02370 USA
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Fax 781 681 2924
www.seronousa.com

February 13, 2002

Susan Allen, M.D.
Director, Division of Reproductive and Urologic
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

BC

NDA 21-322
Luveris™ (lutropin alfa for injection)
Response to FDA Request for Additional Information

Dear Dr. Allen,

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001 and to an Agency telephone call on February 12, 2002 during which the methionine acceptance criteria were discussed by the Chemistry Team Leader.

Please find enclosed herewith the response to the Agency's request for information.

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions about this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, at 781-681-2273, or the undersigned at 781-681-2298.

Yours sincerely,

P.W.J.

Pamela Williamson Joyce
Vice President, US Regulatory Affairs

MEMORANDUM OF TELECON

DATE: February 12, 2002

APPLICATION NUMBER: NDA 21-322, Luveris™ (lutropin alfa for injection)

BETWEEN:

Name: Lisa Mills, Manager, Regulatory Affairs
Phone: (781) 681 - 2273
Representing: Serono, Inc.

AND

Name: David Lin, Ph.D., Chemistry Team Leader
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Request for additional chemistry information from the sponsor.

Background:
Luveris™ (lutropin alfa for injection) is indicated for concomitant administration with r-hFSH for the induction of ovulation in infertile women with severe LH deficiency. This drug was investigated clinically under IND 44,108 and included reports of other studies not conducted under an IND and without input from FDA. The NDA was received on May 1, 2001. The primary User Fee goal date for this application is March 1, 2001.

Discussion:
Concerning the sponsor's response to include methionine content as a release test and in the stability protocol, the justification for the proposed acceptance criteria of [ ] was not provided. The Agency stated that a proposed acceptance criterion of [ ] might be more appropriate.

Decision Reached: The sponsor will provide a justification.

Action Items:
The sponsor will submit the requested information as an amendment to the NDA.

Addendum: Based on information provided by the sponsor, a T-con on February 13, 2002 to discuss the proposed methionine content acceptance criteria. It was stated that based on the limited data available in the NDA, the Agency recommends a tentative acceptance criteria of [ ], at both release and during stability testing. The sponsor will provide a response to the Agency's recommendation as an amendment to the NDA.

/S/

David Lin, Ph.D.
Chemistry Team Leader

cc:
NDA 21-322
HFD-580/Division Files
HFD-580/Reddy/Lin

Created by: David Lin, February 12, 2002
Concurrence:
Finalized: 2/14/02

TELECON MINUTES

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/s/

David T. Lin
2/14/02 10:20:13 AM
CHEMIST

DUPLICATE

CONFIDENTIAL

serono

NDA ORIG AMENDMENT

Serono, Inc.
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Rockland, MA 02370 USA
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February 11, 2002

Susan Allen, M.D.
Director, Division of Reproductive and Urologic
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

10-BC

NDA 21-322
Luveris™ (lutropin alfa for injection)
Response to FDA Request for Additional Information

Dear Dr. Allen,

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001 and to an Agency telephone call on February 7, 2002 during which additional information was requested by the Chemistry Team Leader.

Please find enclosed herewith responses to the Agency's request for information.

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions about this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, at 781-681-2273, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President, US Regulatory Affairs

DRAFT

MEETING MINUTES

Date: February 11, 2002 **Time:** 2:00 - 3:00 PM **Location:** PKLN; Room 17B-43

NDA: 21-322 **Drug Name:** Luveris™ (lutropin alfa for injection)

Indication: Concomitant administration with r-hFSh for the induction of ovulation in infertile women with severe deficiency in LH [illegible]

Type of Meeting: Status Meeting (10-month)

Sponsor: Serono Laboratories, Inc.

Meeting Chair: Shelley Slaughter, M.D., Ph.D.

Meeting Recorder: Archana Reddy, M.P.H.

FDA Attendees:
Shelley Slaughter, M.D., Ph.D. – Acting Deputy Director, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
Ridgely Bennett, M.D., M.P.H. – Medical Officer, DRUDP (HFD-580)
Archana Reddy, M.P.H. – Regulatory Project Manager, DRUDP (HFD-580)
David Lin, Chemistry Team Leader, Ph.D., Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
DJ Chatterjee, Ph.D. – Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objectives: Labeling meeting

Background: Luveris™ (lutropin alfa for injection) is indicated for concomitant administration with r-hFSH for the induction of ovulation in infertile women with severe LH [illegible] deficiency. This drug was investigated clinically under IND 44,108 and included reports of other studies not conducted under an IND and without input from FDA. The NDA was received on May 1, 2001. The primary User Fee goal date for this application is March 1, 2001.

Decisions Reached:
Clinical
- The following dates were agreed upon as due dates for reviews and action package:
  - February 1, 2001 – all reviews should be given to the Clinical Team Leader (reviews due at this time should be final)
  - February 15, 2001 – Final Reviews and Action Package are due to the Division Director
- Medical Reviewer noted that review is still on-going
- clinical team leaning towards a not approvable action
- references to excessive follicular development need to be reworded in the label

Statistics
- draft review ongoing

- the reviewer will look at OHSS risk by subgroup
- p values in Study 21008 are acceptable but p values for study 6253 and 6905 are not acceptable in label

Pharmacology and Toxicology
- review complete; recommend approval

Microbiology
- review complete; recommend approval

Clinical Pharmacology
- draft review complete; review will be finalized by Monday
- pharmacokinetic reviewer will revise the Clinical Pharmacology section of the label

Chemistry
- draft review complete; approvable pending inspection report and microbiology review
- EES final report/recommendation pending
- Line 392 of the label should be reworded and labeling for the abdomen only should be included

DSI
- inspection of all four sites is complete; Inspection Summary completed by DSI

OPDRA Tradename Review
- review complete; tradename found to be acceptable

Action Items:
1) The reviewers will finalize all changes to the label by Friday, February 15, 2002.

/S/ /S/

Signature, minutes preparer Concurrence, Chair

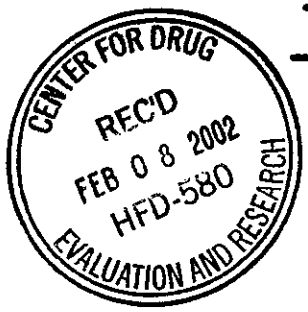
Cc: Arch
HFD-580/Division Files
HFD-580/Slaughter/Shames/Bennett/Welch/Meaker/Parekh/Chatterjee/Raheja/Jordan/Lin/Reddy/
HFD-805/Riley

Drafted by: Archana Reddy, February 11, 2002
Concurrence: djc/February , 2002, km/February 12, 2002, dl/February 12, 2002, rb/February 12, 2002, ss/February , 2002
Finalized: Archana Reddy,

MEETING MINUTES

CONFIDENTIAL

DUPLICATE



serono

February 7, 2002

Susan Allen, M.D.
Director, Division of Reproductive and Urologic
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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ORIG AMENDMENT

BM

NDA 21-322
Luveris™ (lutropin alfa for injection)
Response to FDA Request for Additional Information

Dear Dr. Allen,

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001 and to an Agency telephone call on February 6, 2002 during which copies of additional Case Report Forms were requested by the Medical Reviewer.

Please find enclosed herewith copies of 37 Case Report Forms of all patients (32) in all studies in all cycles whose treatment was cancelled due to the risk of Ovarian Hyperstimulation Syndrome (OHSS).

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions about this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, at 781-681-2273, or the undersigned at 781-681-2298.

Yours sincerely,

P.W.J.

Pamela Williamson Joyce
Vice President, US Regulatory Affairs

MEMORANDUM OF TELECON

DATE: February 7, 2002

APPLICATION NUMBER: NDA 21-322, Luveris™ (lutropin alfa for injection)

BETWEEN:

Name: Lisa Mills, Manager, Regulatory Affairs
Phone: (781) 681 - 2273
Representing: Serono, Inc.

AND

Name: Archana Reddy, M.P.H., Project Manager
David Lin, Ph.D., Chemistry Team Leader
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Request for additional chemistry information from the sponsor.

Background:
Luveris™ (lutropin alfa for injection) is indicated for concomitant administration with r-hFSH for the induction of ovulation in infertile women with severe LH [ ] deficiency. This drug was investigated clinically under IND 44,108 and included reports of other studies not conducted under an IND and without input from FDA. The NDA was received on May 1, 2001. The primary User Fee goal date for this application is March 1, 2001.

Discussion:

1) In the analytical methods section, no detailed description of [ ] immunoassay is provided.
   Decision Reached: The sponsor will provide a detailed description of the [ ] immunoassay.
2) [ ]

   The sponsor should clearly identify when the study completion is anticipated.
   Decision Reached: The sponsor committed to provide information [ ]
3) The sponsor should add the following statement to the stability commitment to the January 17, 2001 submission:
   Serono will conduct stability studies on the first three commercial batches in accordance with the study protocol.
   Decision Reached: The sponsor agreed to add this statement to this submission.
4) Given that methionine is important for the stability of the drug product, the sponsor should commit to continuing the assay for methionine content with acceptance criteria during stability and to performing a methionine assay at release. Reduced testing during stability is acceptable. It is possible that in the future the sponsor could eliminate this methionine test in the stability protocol.

Decision Reached: The sponsor agreed to the assay for methionine content with acceptance criteria during stability and to performing a methionine assay at release, with the possibility of eliminating later testing for methionine during stability, in the future.

Action Items:

1) The sponsor will submit the requested information as an amendment to the NDA.

/S/

David Lin, Ph.D.
Chemistry Team Leader

Cc:
Arch NDA
HFD-580/Division Files
HFD-580/Reddy/Lin

Created by: Archana Reddy, February 8, 2002
Concurrence: David Lin, February 8, 2002
Finalized: Archana Reddy, February 8, 2002

TELECON MINUTES

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/s/

David T. Lin
2/11/02 03:22:02 PM
I concur.

MEETING MINUTES

Date: February 4, 2002 **Time:** 1:00 – 2:15 PM **Location:** PKLN; Room 17B-43

NDA: 21-322 **Drug Name:** Luveris™ (lutropin alfa for injection)

Indication: Concomitant administration with r-hFSh for the induction of ovulation in infertile women with severe deficiency in LH [illegible]

Type of Meeting: Status Meeting (10-month)

Sponsor: Serono Laboratories, Inc.

Meeting Chair: Shelley Slaughter, M.D., Ph.D.

Meeting Recorder: Archana Reddy, M.P.H.

FDA Attendees:
Shelley Slaughter, M.D., Ph.D. – Acting Deputy Director, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
Ridgely Bennett, M.D., M.P.H. – Medical Officer, DRUDP (HFD-580)
Archana Reddy, M.P.H. – Regulatory Project Manager, DRUDP (HFD-580)
David Lin, Chemistry Team Leader, Ph.D., Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
DJ Chatterjee, Ph.D. – Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objectives: Labeling meeting

Background: Luveris™ (lutropin alfa for injection) is indicated for concomitant administration with r-hFSH for the induction of ovulation in infertile women with severe LH [illegible] deficiency. This drug was investigated clinically under IND 44,108 and included reports of other studies not conducted under an IND and without input from FDA. The NDA was received on May 1, 2001. The primary User Fee goal date for this application is March 1, 2001.

Decisions Reached:
Clinical

- The following dates were agreed upon as due dates for reviews and action package:
  - February 1, 2001 – all reviews should be given to the Clinical Team Leader (reviews due at this time should be final)
  - February 15, 2001 – Final Reviews and Action Package are due to the Division Director
- Medical Reviewer noted that review is still on-going
- clinical team leaning towards a not approvable action
- OHSS considered a treatment success according to sponsor; Division does not agree that OHSS is a treatment success
- Clinical Team Leader will brief Division Director on the status of the application/label

- Not sufficient information to show that drug is better than placebo

Statistics
- draft review complete
- the reviewer will look at OHSS risk by subgroup

Pharmacology and Toxicology
- review complete; recommend approval

Microbiology
- review complete; secondary review pending

Clinical Pharmacology
- draft review complete
- pharmacokinetic reviewer will revise the Clinical Pharmacology section of the label

Chemistry
- draft review complete; approvable pending inspection report and microbiology review
- EES final report/recommendation pending
- testing for methionine only in the development process is not acceptable because methionine contributes to the stability of the drug product
- Container/Carton Labels – Recommend relocating statement "75 I.U." to appear beneath the established name with asterisk and statement to define the asterisk

DSI
- inspection of all four sites is complete; Inspection Summary completed by DSI

OPDRA Tradename Review
- review complete; tradename found to be acceptable

Action Items:
1) The PM will finalize the revisions to the draft proposed labeling by Friday, February 7, 2002.

/S/

Signature, minutes preparer

/S/

Concurrence, Chair

Cc: Arch
HFD-580/Division Files
HFD-580/Slaughter/Shames/Bennett/Welch/Meaker/Parekh/Chatterjee/Raheja/Jordan/Lin/Reddy/
HFD-805/Riley

Drafted by: Archana Reddy, February 5, 2001
Concurrence: djc/February 6, 2002, km/February 6, 2002, dl/February 6, 2002, rb/February 6, 2002, ss/February 7, 2002
Finalized: Archana Reddy, February 7, 2002

MEETING MINUTES

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/s/

Shelley Slaughter
2/11/02 12:06:13 PM
I concur

CONFIDENTIAL

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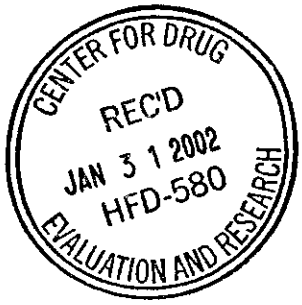

Serono, Inc.
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Rockland, MA 02370 USA
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January 30, 2002

Susan Allen, M.D.
Director, Division of Reproductive and Urologic
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

BC

NDA ORIG AMENDMENT

NDA 21-322
Luveris™ (lutropin alfa for injection)
Response to FDA Request for Additional Information

Dear Dr. Allen,

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001, to an Agency telephone call on January 17, 2002 during which additional information was requested by the Chemistry Team Leader, and to an Agency telephone call on January 22, 2002 with the Chemistry Team Leader during which it was agreed that the executed batch records in French are acceptable.

Please find enclosed herewith responses to the Agency's request for information.

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions about this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, at 781-681-2273, or the undersigned at 781-681-2298.

Yours sincerely,

P.W.J.

Pamela Williamson Joyce
Vice President, US Regulatory Affairs

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NDA ORIG AMENDMENT

N - 515

Serono, Inc.
One Technology Place
Rockland, MA 02370 USA
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January 29, 2002

Susan Allen, M.D.
Director, Division of Reproductive and Urology
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 21-322
Luveris™ (lutropin alfa for injection)
Response to FDA Request for Information

Dear Dr. Allen,

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001 and to a January 29, 2002 Agency telephone call during which the location for information on r-hLH and r-hFSH being mixed and injected in PK Study 6137 was requested.

The information on r-hLH and r-hFSH being combined in 1 mL of water for injection and administered as a single subcutaneous injection is located in NDA 21-322 / Volume 49, pages 012, 015, 016 from the Study Report for PK Study 6137. Copies of the relevant pages are attached for your convenience.

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions about this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, at 781-681-2273, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President, US Regulatory Affairs

CONFIDENTIAL

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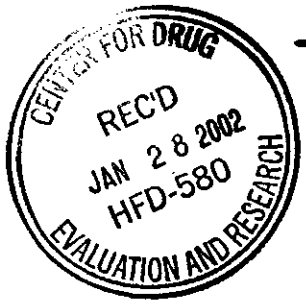

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January 25, 2002

Susan Allen, M.D.
Director, Division of Reproductive and Urologic
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

BL

NDA 21-322
Luveris™ (lutropin alfa for injection)
Response to FDA Request for Additional Information

Dear Dr. Allen,

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001 and to Agency telephone calls on January 15, 2002 and January 24, 2002 during which additional information was requested by the Microbiology Reviewer.

Please find enclosed herewith responses to the Agency's request for information.

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions about this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, at 781-681-2273, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President, US Regulatory Affairs

Confidential

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DUPLICATE

January 24, 2002

Susan Allen, M.D.
Director, Division of Reproductive and Urology
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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www.seronousa.com

BT
NDA ORIG AMENDMENT

NDA 21-322
Luveris™ (lutropin alfa for injection)
Amendment to Pending NDA

Dear Dr. Allen,

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001, to an Amendment dated December 21, 2001 providing marketing authorization information, to a December 31, 2001 Agency telephone call during which a list of the countries in which Luveris has been sold was requested, and to a January 17, 2002 Agency telephone call during which the launch dates and available post-marketing safety information in those countries were requested.

As of January 2, 2002, Luveris™ (82.5 IU lutropin alfa, 48 mg sucrose, 0.83 mg dibasic sodium phosphate dihydrate, 0.052 mg monobasic sodium phosphate monohydrate, 0.050 mg polysorbate 20) has been launched and sold in the following countries:

Country	Launch Date
Italy	May 2001
Germany	July 2001
U.K.	September 2001
Sweden	October 2001
Denmark	October 2001
Norway	October 2001
Finland	October 2001
Spain	November 2001
Mexico	November 2001

Based on figures from clinical trials and sales data, it can be estimated that about — patients received Luveris treatment from the end of November 2000 to the end of November 2001.

As of January 15, 2002, no post-marketing (spontaneous) adverse event reports have been received by Serono.

Table 1 below summarizes the adverse event reports received between November 29, 2000 and November 28, 2001.

Table 1: Numbers of Reports by Source and by Type

SOURCE	SERIOUS		NON-SERIOUS
	Labelled/ Expected	Unlabelled/ Unexpected	Unlabelled
Spontaneous AE	0	0	0
Literature	0	0	0
Clinical Trials	3	0	not included
Sub-Total	**3**	**0**	**0**
TOTAL	**3***		**0**

* All of these reports were received in clinical studies in indications other than the indication which is the subject of the NDA and at higher doses than the proposed dose. Copies of the MedWatch Forms are provided in Attachment 1.

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions about this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, at 781-681-2273, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President, US Regulatory Affairs

1/25/02

45 Day Meeting Checklist
CLINICAL

ITEM	YES	NO	COMMENT
1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?	✓		
2) Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	✓		
3) On its face, is the clinical section of the NDA legible so that substantive review can begin?	✓		
4) If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	To the extent agreed to previously		
5) On its face, do there appear to be the requisite number of adequate and well controlled studies in the application?	✓		
6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	✓		
7) Are all data sets for pivotal efficacy studies complete for all indications (infections) requested?	CD		
8) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	To the extent agreed to previously		

ITEM	YES	NO	COMMENT
9) Has the applicant submitted line listings in a format to allow reasonable review of the patient data. Has the applicant submitted line listings in the format agreed to previously by the Division?	✓		
10) Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	Not needed.		
11) Has the applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division?	✓		
12) Has the applicant presented the safety data in a manner consistent with center guidelines and/or in a manner previously agreed to by the Division?	✓		
13) Has the applicant presented a safety assessment based on <u>all</u> current world-wide knowledge regarding this product?	✓		
14) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package?	✓		
15) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	✓		
16) From a clinical perspective, is this NDA fileable? If "no", please state in item #17 below why it is not.	✓		

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/s/

Ridgely C. Bennett
1/25/02 11:37:23 AM
MEDICAL OFFICER

MEMORANDUM OF TELECON

DATE: January 17, 2002

APPLICATION NUMBER: NDA 21-322, Luveris™ (lutropin alfa for injection)

BETWEEN:

Name: Lisa Mills, Manager, Regulatory Affairs
Phone: 781-659-2338
Representing: Serono, Inc.

AND

Name: Archana Reddy, M.P.H., Project Manager
Ridgely Bennett, M.D., M.P.H., Medical Officer
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: To request clinical information from the sponsor.

Discussion:
The sponsor agreed to provide the following information:

1) The actual date the drug was marketed in each country where marketing authorization was received.
2) Safety data from all countries in which the drug has been launched.

/S/

Ridgely Bennett, M.D., M.P.H.
Medical Officer

Cc:
Arch NDA
HFD-580/Division Files
HFD-580/Reddy/Bennett

Created by: Archana Reddy, January 23, 2002
Concurrence: Ridgely Bennett, January 23, 2002
Finalized: Archana Reddy, January 24, 2002

Teleconference Minutes

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/s/

Archana Reddy
1/28/02 12:15:23 PM
CSO
1/17/02 mm

Ridgely C. Bennett
1/29/02 09:25:09 AM
MEDICAL OFFICER
I concur.

CONFIDENTIAL

Serono, Inc.
One Technology Place
Rockland, MA 02370 USA
Tel. 781 982 9000
Fax 781 681 2924
www.seronousa.com

January 10, 2002

Susan Allen, M.D.
Director, Division of Reproductive and Urologic
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 21-322
Luveris™ (lutropin alfa for injection)
Response to Information Request Letter

Dear Dr. Allen,

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001 and to a January 8, 2002 FAX in which information on the SAS datasets was requested.

Please find attached responses to the request for statistical information.

Should you have any additional questions regarding the statistical information, please contact Lisa S. Mills, Manager, Regulatory Affairs at 781-681-2273 to arrange a teleconference with the statisticians to discuss the information.

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Yours sincerely,

Pamela Williamson Joyce
Vice President, US Regulatory Affairs

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 8, 2002

To: Lisa Mills Manager, Regulatory Affairs	**From:** Archana Reddy, M.P.H. Regulatory Project Manager
Company: Serono, Inc.	Division of Division of Reproductive and Urologic Drug Products
Fax number: 781-681-2924	**Fax number:** 301-827-4260
Phone number: 781-681-2273	**Phone number:** 301-827-4260

Subject: Fax of statistical questions regarding variables in datasets for the four supporting studies

Total no. of pages including cover: 2

Comments:

Lisa,

Please provide a reply to the attached statistical questions for Luveris. If there are any questions, the statistician can provide further clarification of the requests.

Thank you,

Archana

Document to be mailed: ☐ YES ☑ NO

Request for Statistical Information

NDA: 21-322
Drug: Luveris™ (lutropin alfa for injection)
Sponsor: Serono, Inc.

Serono submitted a CD containing SAS datasets dated April 30, 2001. The following request is in reference to matching the data set variables to the efficacy results presented in the study reports for the four supporting studies (6253, 6905, 7798, and 8297). For each of the 4 supporting studies separately, please provide documentation identifying the SAS dataset and variable name, which corresponds to the following:

1) Treatment group (with list of dose group codes)
2) Intent-to-treat patient Y/N?
3) Evaluable patient Y/N?
4) Primary efficacy – largest follicle size
5) Primary efficacy – largest follicle ≥ 17 mm Y/N?
6) Primary efficacy – final E2 value
7) Primary efficacy – final E2 ≥ 109 pg/mL Y/N?
8) Primary efficacy – final P4 value
9) Primary efficacy – final P4 ≥ 7.9 ng/mL Y/N?
10) Primary efficacy – follicular development Y/N?
11) Primary efficacy – Chemical pregnancy Y/N?
12) Primary efficacy - Clinical pregnancy Y/N?
13) Primary efficacy – OHSS risk Y/N?

MEETING MINUTES

Date: January 7, 2002 **Time:** 2:00 – 3:00 PM **Location:** PKLN; Room 17B-43

NDA: 21-322 **Drug Name:** Luveris™ (lutropin alfa for injection)

Indication: Concomitant administration with r-hFSh for the induction of ovulation in infertile women with severe deficiency in LH

Type of Meeting: Status Meeting (9-month)

Sponsor: Serono Laboratories, Inc.

Meeting Chair: Shelley Slaughter, M.D., Ph.D.

Meeting Recorder: Archana Reddy, MPH

FDA Attendees:
Shelley Slaughter, M.D., Ph.D. – Medical Team Leader, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
Ridgely Bennett, M.D. – Medical Officer, DRUDP (HFD-580)
Archana Reddy, MPH – Regulatory Project Manager, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
DJ Chatterjee, Ph.D. – Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objectives: To discuss the status of the reviews for this pending NDA.

Background: Luveris™ (lutropin alfa for injection) is indicated for concomitant administration with r-hFSH for the induction of ovulation in infertile women with severe LH deficiency. This drug was investigated clinically under IND 44,108 and included reports of other studies not conducted under an IND and without input from FDA. The NDA was received on May 1, 2001. The primary User Fee goal date for this application is March 1, 2001.

Decisions Reached:
Clinical
- The following dates were agreed upon as due dates for reviews and action package:
  - February 1, 2001 – all reviews should be given to the Clinical Team Leader (reviews due at this time should be final)
  - February 15, 2001 – Final Reviews and Action Package are due to the Division Director
- Medical Reviewer noted that review is still on-going
- no decision on the approvability of the drug product has been made
- Medical Officer will pull together recommendations to the sponsor from prior meetings in the review

Statistics
- the reviewer requested the PM fax questions about the variables in the data sets to the sponsor

- data sets for the four supporting studies (6253, 6905, 7798, and 8297) are poorly organized and documented; difficult to go from the study reports to the actual data
- review on primary efficacy data can be completed
- data for pivotal study 21008 (U.S. study) is presented in an acceptable manner

Pharmacology and Toxicology
- review is pending; no issues noted at this time

Microbiology
- review is pending; no issues noted at this time

Clinical Pharmacology
- review is pending
- the to-be-marketed (new) formulation also has an extra component in L-methionine [ ] compared to the clinical trial formulation; this, in addition [ ] are the two intended changes post clinical trials
- PK parameters are acceptable
- Study drug meets bioequivalence criteria
- Other studies (dose proportionality, comparative report, study of 115 I.U. with and without FSH) are acceptable
- LH may have assay problems

Chemistry
- review will be complete in approximately one week
- EES final report/recommendation pending

DSI
- inspection of all four sites is complete; Inspection Summary completed by DSI

OPDRA Tradename Review
- review complete; tradename found to be acceptable

Action Items:
1) The PM will fax a list of questions about the variables in the data sets to the sponsor (completed on January 8, 2002).
2) The PM will research information on regulations for Orphan Drugs and approvability issues.
3) The pharmacokinetic reviewer will follow-up on [ ] issue with the chemistry reviewer or via a teleconference with the sponsor.

Signature, minutes preparer

Concurrence, Chair

Cc: Arch
HFD-580/Division Files
HFD-580/Slaughter/Shames/Bennett/Welch/Meaker/Parekh/Chatterjee/Raheja/Jordan/Lin/Reddy/
HFD-805/Riley

Drafted by: Archana Reddy, January 9, 2001
Concurrence: km/January 11, 2002, ap/January 16, 2002, djc/January 17, 2002, ss/January 22, 2002, rb/January 22, 2002
Finalized: Archana Reddy, January 24, 2002

MEETING MINUTES

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

/s/

Shelley Slaughter
2/5/02 04:15:31 PM
I concur.

Confidential

serono

DUPLICATE

Serono, Inc.
One Technology Place
Rockland, MA 02370 USA
Tel. 781 982 9000
Fax 781 681 2924
www.seronousa.com

January 3, 2002

Susan Allen, M.D.
Director, Division of Reproductive and Urology
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

BC
NDA ORIG AMENDMENT

NDA 21-322
Luveris™ (lutropin alfa for injection)
Amendment to Pending NDA

Dear Dr. Allen,

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001, to an Amendment dated December 21, 2001 providing marketing authorization information, and to a December 31, 2001 Agency telephone call requesting the countries in which Luveris has been sold.

As of January 2, 2002, Luveris™ (82.5 IU lutropin alfa, 48 mg sucrose, 0.83 mg dibasic sodium phosphate dihydrate, 0.052 mg monobasic sodium phosphate monohydrate, 0.050 mg polysorbate 20) has been sold in the following countries:

Country
Italy
Germany
U.K.
Sweden
Denmark
Norway
Finland
Spain, Mexico

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions about this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, at 781-681-2273, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson-Joyce
Vice President, US Regulatory Affairs

5 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

12/26/01

4 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

12-21-01

83 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

12-13-01

Screening of New NDA
Division of Biometrics II

Date: 6/4/01

NDA #: 21-322

Priority Classification: 3S

Trade Name: Luveris 75IU

Applicant: Serono

Generic Name: lutropin alpha for injection

Date of Submission: 5/1/01

Indication: concomitant administration with r-hFSH for the induction of ovulation in infertile women with severe LH deficiency

No. of Controlled Studies: 4

User Fee Goal Date: 3/1/02

Date of 45-Day Meeting: 6/6/01

Medical Officer: Ridgely Bennett, M.D. (HFD-580)

Project Manager: Archana Reddy

Screened by: Kate Meaker, M.S.

Volume numbers in statistical section: 1.1, 1.2, 1.73 – 1.86

Anticipated Review Completion Date: 1/1/02

Comments:

1. This IND 44,108 received orphan drug status.

2. I will ask the PM to request a new copy of the CD with SAS datasets which was provided in Vol. 1.73. The original CD was not readable. Also, an archival copy of the SAS datasets must be submitted to the electronic document room.

3. It is fileable.

CHECKLIST

Item	**Check (NA if not applicable)**
Index sufficient to locate necessary reports, tables, etc.	**Yes**
Original protocols & subsequent amendments available in the NDA	**Yes**
Designs utilized appropriate for the indications requested	**Yes**
Endpoints and methods of analysis spelled out in the protocols	**Yes**
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	**NA**
Appropriate references included for novel statistical methodology (if present)	**NA**
Sufficient data listings and intermediate analysis tables to permit statistical review	**Yes**
Data from primary studies on diskettes and/or CANDA submitted	**CD**
Intent-to-treat analysis	**Yes**
Effects of dropouts on primary analyses investigated	**No**
Safety and efficacy for gender, racial, and geriatric subgroups investigated	**NA**

BRIEF SUMMARY OF CONTROLLED CLINICAL TRIALS

Study Number (Dates Conducted)	Number of Centers (Locations)	Total Sample Size	Type of Control	Design	Duration of Treatment
21008 (2/00 – 9/00)	25 (US, Canada, Israel, Australia)	30 Luveris 75IU n=20 Placebo n=10	Placebo	Randomized, Placebo-control, Double-blind, Multicenter, Parallel arm	1 cycle
6253 (9/93 – 4/95)	10 (Europe, Israel)	38 Luveris 25IU n=8 Luveris 75IU n=11 Luveris 225IU n=10 Placebo n=9	Placebo	Randomized, Placebo-control, Open-label, Multicenter, Parallel arm	1 to 3 cycles; Only randomized to first cycle; First cycle is primary for efficacy
6905 (7/94 – 7/97)	14 (US)	40 Luveris 25IU n=9 Luveris 75IU n=11 Luveris 225IU n=9 Placebo n=11	Placebo	Randomized, Placebo-control, Open-label, Multicenter, Parallel arm	1 to 3 cycles; Only randomized to first cycle; First cycle is primary for efficacy
7798 (9/95 – 5/98)	7 (Germany)	15 (First cycle dose:) Luveris 25IU n=5 Luveris 75IU n=5 Luveris 225IU n=5	Dose-ranging; 3 dose levels of Luveris	Randomized, Dose-ranging, Open-label, Multicenter, Crossover	1 to 3 cycles Randomized to a sequence of 3 doses; First cycle is primary for efficacy

_____

Statistical Reviewer

Concur: Dr. Welch

cc:
Archival NDA #21-322
HFD-580
HFD-580/RBennett, SAllen
HFD-715/ENevius, MWelch, KMeaker

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

/s/

Katherine Meaker
6/5/01 01:49:36 PM
BIOMETRICS

Mike Welch
6/5/01 02:31:59 PM
BIOMETRICS
concur

NDA 20-322
Luveris™ (lutropin alfa for injection) 75 IU
Serono, Inc.

User Fee Information

This NDA has an orphan drug indication. Therefore, the User Fee payment is exempt.

5/15/01

Division of Reproductive and Urologic Drug Products

ADMINISTRATIVE REVIEW OF APPLICATION

Application Number: **21-322**

Name of Drug: Luveris™ (lutropin alfa for injection)

Sponsor: Serono, Inc.

Material Reviewed: NDA 21-322

Submission Date: April 30, 2001

Receipt Date: May 1, 2001

Filing Date: June 30, 2001

User-Fee Goal Date(s): March 1, 2002 and May 1, 2002

Proposed Indication: For concomitant administration with r-hFSH for stimulation of follicular development and the induction of ovulation in infertile women with severe LH deficiency

Other Background Information: IND 44,108

Review

PART I: OVERALL FORMATTING[a]

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Cover Letter (original signature)	X		Volume 1
2. Form FDA 356h (original signature)	X		Volume 1
a. Reference to DMF(s) & Other Applications	X		Volume 1, page 1 of 356h
3. Patent information & certification	X		Volume 1, pages 25-56
4. Debarment certification (note: must have a definitive statement)	X		Volume 1, page 58
5. Financial Disclosure	X		Volume 1, pages 66-76

6. Comprehensive Index	X		Volume 1, page i
7. Pagination	X		throughout
8. Summary Volume	X		Volume 2. pages 35-289
9. Review Volumes	X		Volumes 3 - 92
10. Labeling (PI, container, & carton labels)	X		
a. unannotated PI	X		Volume 1, page 90-116
b. annotated PI	X		Volume 2, pages 2-28
c. immediate container	X		Volume 1, page 88
d. carton	X		Volume 1, pages 83-87
e. foreign labeling (English translation)		X	This drug is not currently being marketed in any country
11. Foreign Marketing History	X		Volume 2, page 34
12. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X		Volume 87, pages 1-139 through Volume 91, page 243
13. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	X		Volume 92, page 1-268 through Volume 93, page 260

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b]

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	X		Class-- Volume 2, page 30 Rationale- Volume 2, page 30 Use—Volume 2, page 32 Benefit—Volume 2, page 32
2. Summary of Each Technical Section			
a. Chemistry, Manufacturing, & Controls (CMC)	X		Volume 2, pages 35-69
b. Nonclinical Pharmacology/Toxicology	X		Volume 2, pages 70-107
c. Human Pharmacokinetic & Bioavailability	X		Volume 2, pages 108-128
d. Microbiology	X		Volume 2, page 130
e. Clinical Data & Results of Statistical Analysis	X		Volume 2, pages 132- 249
3. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	X		Volume 2, pages 251-289
4. Summary of Safety	X		Volume 2, pages 269-273
5. Summary of Efficacy	X		Volume 2, page 268

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c]

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. List of Investigators	X		Volume 55, pages 2-25
2. Controlled Clinical Studies	X		Volume 2, page 181 and Volume 55
a. Table of all studies	X		Volume 2, page 182 and Volume 55, page 45
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	X		Reports of individual studies—Volume 155, page 152-154; 162-195 Statistical report—Volume 73, page 7-65 Ongoing studies—Volume 55, page 75
c. Optional overall summary & evaluation of data from controlled clinical studies	X		Volume 2, page 268
3. Integrated Summary of Efficacy (ISE)	X		Volume 56
4. Integrated Summary of Safety (ISS)	X		Volume 56, pages 73-96
5. Drug Abuse & Overdosage Information	X		Volume 2, page 249
6. Integrated Summary of Benefits & Risks of the Drug	X		Volume 2, page 264
7. Gender/Race/Age Safety & Efficacy Analysis Studies	X		Volume 56, page 97 (demographics)

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population		X	
2. Diskettes			
a. Proposed unannotated labeling in MS WORD 8.0		X	
b. Stability data in SAS data set format		X	
c. Efficacy data in SAS data set format		X	
d. Biopharmacological information & study summaries in MS WORD 8.0		X	
e. Animal tumorigenicity study data in SAS data set format		X	
3. User-fee payment receipt		X	This NDA is exempt from user fees as it is an orphan indication.

Y=Yes (Present), N=No (Absent)

[a]"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[b]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[c]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

Additional Comments: This NDA is for an Orphan Drug Indication.

Conclusions: This NDA can be filed from a regulatory perspective.

_____
Regulatory Health Project Manager

_____
Concurrence

cc:
Original NDA
HFD-580/Div. Files
HFD-580/PM/D.Moore/T.Rumble
HFD-580/S.Allen/D.Shames
HFD-580/ S.Slaughter/R.Bennett/M.Rhee/A.Jordan/K.Raheja/A.Parekh
draft: May 14, 2001
final: May 15, 2001

ADMINISTRATIVE REVIEW

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

/s/

Diane V. Moore
5/15/01 05:38:21 PM
CSO

Terri F. Rumble
5/16/01 04:35:55 PM
CSO

3 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

6-11-01

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Serono, Inc.
100 Longwater Circle
Norwell, MA 02061 USA

2. TELEPHONE NUMBER *(Include Area Code)*

(781) 982-9000

3. PRODUCT NAME

Luveris

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☑ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____
(APPLICATION NO. CONTAINING THE DATA)

5. USER FEE I.D. NUMBER

4034

6. LICENSE NUMBER / NDA NUMBER

NDA 21-322

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☑ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☑ NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	Vice President, Regulatory Affairs	April 30, 2001

FORM FDA 3397 (5/98)

18. USER FEE WAIVER

On October 7, 1994, Luveris™ was granted orphan-drug designation (application number for the indication that is the subject of this NDA.

A copy of the designation letter from the Office of Orphan Product Development is provided on the following pages.

Under section 736(a)(1)(E) of the FD&C Act, this original New Drug Application (NDA) is not subject to an application fee since Luveris™ is indicated for a rare disease or condition designated under section 526 of the FD&C Act (orphan drug designation). This NDA does not include an indication that is not so designated.

Appears This Way
On Original

5/15/01

Division of Reproductive and Urologic Drug Products

ADMINISTRATIVE REVIEW OF APPLICATION

Application Number: 21-322

Name of Drug: Luveris™ (lutropin alfa for injection)

Sponsor: Serono, Inc.

Material Reviewed: NDA 21-322

Submission Date: April 30, 2001

Receipt Date: May 1, 2001

Filing Date: June 30, 2001

User-Fee Goal Date(s): March 1, 2002 and May 1, 2002

Proposed Indication: For concomitant administration with r-hFSH for stimulation of follicular development and the induction of ovulation in infertile women with severe LH deficiency

Other Background Information: IND 44,108

Review

PART I: OVERALL FORMATTING[a]

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2. Form FDA 356h (original signature)	X		Volume 1
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4. Debarment certification (note: must have a definitive statement)	X		Volume 1, page 58
5. Financial Disclosure	X		Volume 1, pages 66-76

6. Comprehensive Index	X		Volume 1, page i
7. Pagination	X		throughout
8. Summary Volume	X		Volume 2. pages 35-289
9. Review Volumes	X		Volumes 3 - 92
10. Labeling (PI, container, & carton labels)	X		
a. unannotated PI	X		Volume 1, page 90-116
b. annotated PI	X		Volume 2, pages 2-28
c. immediate container	X		Volume 1, page 88
d. carton	X		Volume 1, pages 83-87
e. foreign labeling (English translation)		X	This drug is not currently being marketed in any country
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12. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X		Volume 87, pages 1-139 through Volume 91, page 243
13. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	X		Volume 92, page 1-268 through Volume 93, page 260

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b]

Y=Yes (Present), N=No (Absent)

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a. Chemistry, Manufacturing, & Controls (CMC)	X		Volume 2, pages 35-69
b. Nonclinical Pharmacology/Toxicology	X		Volume 2, pages 70-107
c. Human Pharmacokinetic & Bioavailability	X		Volume 2, pages 108-128
d. Microbiology	X		Volume 2, page 130
e. Clinical Data & Results of Statistical Analysis	X		Volume 2, pages 132- 249
3. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	X		Volume 2, pages 251-289
4. Summary of Safety	X		Volume 2, pages 269-273
5. Summary of Efficacy	X		Volume 2, page 268

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c]

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
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b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	X		Reports of individual studies—Volume 155, page 152-154; 162-195 Statistical report—Volume 73, page 7-65 Ongoing studies—Volume 55, page 75
c. Optional overall summary & evaluation of data from controlled clinical studies	X		Volume 2, page 268
3. Integrated Summary of Efficacy (ISE)	X		Volume 56
4. Integrated Summary of Safety (ISS)	X		Volume 56, pages 73-96
5. Drug Abuse & Overdosage Information	X		Volume 2, page 249
6. Integrated Summary of Benefits & Risks of the Drug	X		Volume 2, page 264
7. Gender/Race/Age Safety & Efficacy Analysis Studies	X		Volume 56, page 97 (demographics)

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population		X	
2. Diskettes			
a. Proposed unannotated labeling in MS WORD 8.0		X	
b. Stability data in SAS data set format		X	
c. Efficacy data in SAS data set format		X	
d. Biopharmacological information & study summaries in MS WORD 8.0		X	
e. Animal tumorigenicity study data in SAS data set format		X	
3. User-fee payment receipt		X	This NDA is exempt from user fees as it is an orphan indication.

Y=Yes (Present), N=No (Absent)

[a]"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[b]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[c]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

Additional Comments: This NDA is for an Orphan Drug Indication.

Conclusions: This NDA can be filed from a regulatory perspective.

Regulatory Health Project Manager

Concurrence

cc:
Original NDA
HFD-580/Div. Files
HFD-580/PM/D.Moore/T.Rumble
HFD-580/S.Allen/D.Shames
HFD-580/ S.Slaughter/R.Bennett/M.Rhee/A.Jordan/K.Raheja/A.Parekh
draft: May 14, 2001
final: May 15, 2001

ADMINISTRATIVE REVIEW

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/s/

Diane V. Moore
5/15/01 05:38:21 PM
CSO

Terri F. Rumble
5/16/01 04:35:55 PM
CSO

Chemistry and Manufacturing Controls

Filing Meeting for NDA 21-322 **June 6, 2001** **David Lin**

Luveris™ (lutropin alfa for injection), 75 IU LH activity per vial
for concomitant administration with r-hFSH for the induction of ovulation in infertile women with severe LH deficiency

Sponsor: Serono, Inc.

Drug Substance

1. Recombinant human luteinising hormone (r-hLH) is a heterodimer glycoprotein, manufactured by Serono S.A. in Switzerland. Consists of two non-covalently linked subunits, designated as the α- and β-subunits. The α-subunit is composed of 92 amino acids containing two N-linked carbohydrate moieties and the β-subunit is composed of 121 amino acids containing a single N-linked carbohydrate moiety.

2. Characterization of r-hLH by: [redacted]

3. Production is a two-part process: 1) mammalian cell culture (Chinese hamster ovary cell line) [redacted] and 2) purification process [redacted]

4. Release tests: [redacted]

5. Stability data: [redacted] full scale batches manufactured at Serono [redacted] and [redacted] pilot scale batches manufactured at development site [redacted]. Sponsor proposes [redacted] re-test period.

Drug Product

1. The drug product is a sterile, white lyophilized pellet contained in [redacted] glass vial with a rubber stopper.

2. The formulation contains 3.7 µg (82.5 IU) r-hLH per mL. The components and composition are:

Component	Quantities
r-hLH	3.7 µg (82.5 IU)[1]
Sucrose	47.75 mg
L-methionine[2]	0.1 mg
Polysorbate 20	0.05 mg
Disodium phosphate dihydrate	0.825 mg
Sodium dihydrogen phosphate monohydrate	0.052 mg
Phosphoric acid (conc.) and/or Sodium hydroxide	To pH 7.0

[redacted]
[2]Methionine ; [redacted]

3. Site of manufacturing and control, primary packaging, stability studies:
   Laboratoires Serono S.A. (LSA)
   Zone Industielle de l'Ouriettaz
   1170 Aubonne, Switzerland

4. The product will be packaged in a [redacted] glass vial. The closure is a [redacted] stopper [redacted] which is then sealed with an aluminum seal ring and a flip off seal cap.

5. Primary Stability data:
   a. 3 commercial scale batches (#51303050, 51304060, 51305060):
      25°C (— months)
      40°C (— months)

   b. Stability of reconstituted product:
      [redacted] at 25°C (with and without Gonal-F)

   Tests performed: [redacted]

[redacted]

6. The sponsor has proposed an expiration dating period — at 25°C.

7. EA: The firm has requested a categorical exclusion.

8. Labeling: The tradename, Luveris, will be consulted to OPDRA for review.

Conclusion:

The information in the CMC section of the NDA is suitable for review.
This NDA may be filed from the CMC point of view.

Requests to the Sponsor:
1. Clarify which facility will perform release and stability testing of the drug product.
2. Are there any light studies conducted on the drug product?
3. Was L-methionine content measured during stability?
4. Are there any results from testing change — during stability?
5. Will additional drug product stability data be submitted during the review cycle.

cc:
NDA 21-322 Division File
HFD-580/AReddy
HFD-580/MJRhee/DLin

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/s/

David T. Lin
6/13/01 02:05:27 PM
CHEMIST

Meeting Minutes

Date: June 6, 2001 **Time:** 2:30 – 3:00 PM **Location:** 17B-43

NDA: 21-322 **Drug:** Luveris™ 75 IU (lutropin alfa for injection)

Indication: Induction of ovulation in infertile women hypogonadotropic hypogonadism.

Sponsor: Serono Inc.

Type of Meeting: Filing Meeting

Meeting Chair: Susan Allen, M.D., MPH

Meeting Recorder: Archana Reddy, MPH

FDA Attendees:
Susan Allen, M.D., MPH, Division Director, DRUDP (HFD-580)
Daniel Shames, M.D, Deputy Director, DRUDP (HFD-580)
Ridgely Bennett, M.D., MPH, Medical Officer, DRUDP (HFD-580)
Terri Rumble, B.S., RN, Chief, Project Management Staff, DRUDP (HFD-580)
Archana Reddy, MPH, Project Manager, DRUDP (HFD-580)
Diane Moore, Project Manager, DRUDP (HFD-580)
Jeanine Best, MSN, RN, Project Manager, DRUDP (HFD-580)
David Lin, Ph.D., Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Krishan Raheja, Ph.D., D.V.M., Pharmacology Reviewer, DRUDP (HFD-580)
Ameeta Parekh, Ph.D., Clinical Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics @ DRUDP (HFD-580)
DJ Chaterjee, Ph.D., Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics @ DRUDP (HFD-580)
Ele Ibarra-Pratt, Division of Scientific Investigations, HFD-42

Meeting Objective: To discuss the fileability of NDA 21-322. The filing date is June 30, 2001.

Background:
Luveris™ 75 IU (lutropin alfa for injection) is a sterile lyophilized powder composed of recombinant human luteinizing hormone, r-hLH. Lutropin alfa for injection is a heterodimeric glycoprotein consisting of two non-covalently linked subunits. This is a recombinant drug product and the new formulation contains methionine. The drug product is an injectable submitted by Serono Inc. for the concomitant administration with r-hFSH for the induction of ovulation in infertile women with severe LH deficiency. The safety and efficacy of the drug product has been examined in five well-

controlled studies for induction of ovulation in women with hypogonadotropic hypogonadism (HH). This is an orphan indication.

Discussion:

Clinical:
- studies 21008 and 6253 are the pivotal studies and studies 6905, 7798, and 8297 are supporting studies contributing primarily safety data
- study 6905 is the original U.S. study using a protocol modified from that originally agreed upon at the pre-NDA meeting
- pivotal study 6253 conducted in Europe; original protocol agreed upon in 1992
- study 7798 is a safety study of 15 patients conducted in Germany and study 8297 is a noncomparative study conducted in Spain
- drug is approved in Europe but has not been marketed yet
- the methionine ingredient in the current formulation was not included in the formulation used in the original studies for this product
- NDA is fileable

Chemistry:
- certain tests, such as [redacted] and methionine content, were not conducted in the stability program
- sponsor is requesting [redacted] of expiration for stability
- NDA is fileable

Pharmacology/Toxicology:
- no issues, NDA is fileable

Biopharmaceutics:
- linking bioequivalence study results with and without methionine have been submitted by the sponsor for review
- the clinical trial formulation is different from the "to-be-marketed" formulation (the latter contains methionine as an additional ingredient)
- NDA is fileable

Statistics:
- no issues, NDA is fileable

Microbiology:
- no issues, NDA is fileable

Other Issues:

DSI – Selection of Study Sites for audit

The following sites were identified by the Medical Officer for DSI audit:

(1) U.S. Sites (Study 21008)
Timothy Yeko (Tampa, Florida)
Laurel Stradtmauer (Cary, NC)

(2) Two out of the following three sites (Study 21008) should be selected for DSI audit:
Robert Kaufmann (Mt. Pleasant, S.C.)
Thomas Vaugh (Austin, TX)
Randall Dunn (Houston, TX)

Decisions made:

- NDA is fileable

Action Items:

(1) The PM will forward the following CMC requests to the sponsor:

  (1) The sponsor should clearly identify which facility will perform release and stability testing of the drug product.
  (2) Are there any light studies conducted on the drug product?
  (3) Was L-methionine content measured during stability?
  (4) Are there any results from testing change [redacted] during stability?
  (5) Will additional drug product stability data be submitted during the review cycle?

(2) Request sponsor to send a copy of labeling being used in the European Union countries. The PM will check if this information is provided in the NDA and ask the sponsor to reference this information.

(3) The PM will finalize the DSI audit form and forward the form to DSI.

/S/

Minutes Preparer: Archana Reddy, MPH

/S/

Concurrence Chair

Cc:
Original NDA 21-322
HFD-580/Division File
HFD-580/PM/Reddy
HFD-580/Allensu/Shamesd/Bennettr/Raheja/Chaterjeed/Lindav/Parekh/Meaker/Rumblet/
HFD-42/Ibarra-Pratt/Molchans
Drafted by:AR/June 6, 2001/nda21322filingminutes.doc
Concurrence:Allen,6.19.2001/Shames,6.19.2001/Rumble,6.07.01/Best,6.12.01//Moore,6.15.01/Best/Chaterjee,6.11.01/Lin,6.12.01/Benett,6.12.01/Raheja,6.11.01

MEETING MINUTES

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/s/

Susan Allen
6/25/01 05:40:15 PM

MEETING MINUTES

Date: October 15, 2001 **Time:** 2:00 - 3:00 PM **Location:** PKLN; Room 17B-43

NDA: 21-322 **Drug Name:** Luveris™ (lutropin alfa for injection)

Indication: Stimulation of follicular development and ovulation in infertile women with severe deficiency in LH

Type of Meeting: Status Meeting (6-month)

Sponsor: Serono Laboratories, Inc.

Meeting Chair: Shelley Slaughter, M.D.

Meeting Recorder: Archana Reddy, MPH

FDA Attendees:
Shelley Slaughter, M.D., Ph.D. – Medical Team Leader, Division of Reproductive and Urologic Drug Products DRUDP (HFD-580)
Ridgely Bennett, M.D. – Medical Officer, DRUDP (HFD-580)
Archana Reddy - Regulatory Project Manager, DRUDP (HFD-580)
David Lin, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Dhruba Chatterjee, Ph.D. - Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objectives: Six-month status meeting for Luveris.

Background: Luveris™ (lutropin alfa for injection) is indicated for concomitant administration with r-hFSH for the induction of ovulation in infertile women with severe LH deficiency. This drug was investigated clinically under IND 44,108. The NDA was received on May 1, 2001. The primary User Fee goal date for this application is March 1, 2001.

Decisions Reached:
Clinical
- The following dates were agreed upon as due dates for reviews and action package:
  - February 1, 2001 – all reviews should be given to the Clinical Team Leader (reviews should be final)
  - February 15, 2001 – Final Reviews and Action Package should be given to the Division Director
- Medical Reviewer noted that review is still on-going
- NDA 21-322 is referencing IND 44,108
- Pre-IND meeting held in 1992; IND submitted by sponsor in 1993 (protocol for the U.S. study submitted only)
- in 1994, the sponsor received orphan drug designation for this indication

- primary endpoint is follicular development
- study 21008 is the pivotal study (75 IU versus placebo) being carried out at 20 different sites in the U.S. using an intent to treat analysis in a total of 39 patients
- ovulation should be clearly defined; sponsor should provide ovulation rate data
- secondary endpoint for efficacy is ovulation as indicated by serum progesterone level in the luteal phase

Chemistry
- review of the application is on-going
- additional stability data will be requested from sponsor

Clinical Pharmacology and Biopharmaceutics:
- the reviewer indicated that there is not much clinical pharmacology data to review and will be able to meet the Feb 1st deadline

Statistics
- the reviewer requested the Medical Officer to provide definitions for preferred endpoints
- a uniform definition of ovulation rates across all IU groups is needed
- the rate is based upon how ovulation is defined; Medical Officer should provide definition of ovulation rate

Pharmacology and Toxicology
- review is pending; no issues noted at this time

DSI
- inspection of all four sites pending

OPDRA Tradename Review
- tradename review is pending

Decisions Reached:
1) All disciplines should complete their final reviews by February 1, 2001.
2) The PM will forward a final package to the Division Director for review on February 15, 2001.

Action Items:
- Project Manager will follow up on the status of the Microbiology and OPDRA Tradename reviews
- Project Manager will check into whether this NDA requires an Office sign-off

/S/

Signature, minutes preparer

/S/

Concurrence, Chair

cc:
NDA Arch:
HFD-580/Reddy/Rumble
HFD-580/SSlaughters/KMeaker/Bennett/Chatterjee/Lin/Welch/Parekh

Drafted: ar/November 29,2001
Concurrences: km/December 17, 2001, dl/December 18, 2001, djc/December 17, 2001, rb/December 17, 2001, ss/December 27, 2001
Finalized: ar/December 31, 2001

MEETING MINUTES

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/s/

Shelley Slaughter
1/2/02 09:46:38 AM
I concur

Teleconference Minutes

Date: November 1, 2001 **Time:** 2 – 2:15 PM **Location:** PKLN 17B-43

Drug: NDA 21-322 **Name:** Luveris™ (lutropoin alfa for injection)

Sponsor: Serono, Inc.

Indication: Stimulation of follicular development and ovulation in infertile women with severe deficiency in LH

Meeting Chair: David Lin, Ph.D.

External Participant Lead: Lisa Mills

FDA Attendees:
Archana Reddy - Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (HFD-580)
David Lin, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

External Participants:
Lisa Mills, Manager, Regulatory Affairs

Meeting Objectives:. To request additional chemistry information from the sponsor.

Background: Luveris™ (lutropin alfa for injection) is indicated for concomitant administration with r-hFSH for the induction of ovulation in infertile women with severe LH . I deficiency. This drug was investigated clinically under IND 44,108. The NDA was received on May 1, 2001. The primary User Fee goal date for this application is March 1, 2001.

Discussion:
1) Volume 11 and 12 (Methods Validation Section)
   Sponsor agreed to resend the following pages from Volume 11: 47, 75, 76, 77, 95,97, 105, 125, and 126.
2) Certificate of Analysis for the excipients used in the product, reagent, and for the drug substance manufacturing should be provided.
3) The sponsor should provide certification that methionine used is from a non-BSE country.
4) DMF cross-referencing vials/stoppers and aluminum seals and a schematic of the vial and the stopper (sizes, diagrams, and dimensions) should be provided.
5) Mock labeling will be provided in PDF format if available.
6) Vial sample will be sent and the clinical study label on this vial used for packaging purposes will be provided.

Cc:
Archival NDA 21-322
HFD-580/Division Files
HFD-580/Reddy/Lin/Rumblet/

Created by: Archana Reddy, December 17, 2001
Concurrence: David Lin, December 26, 2001
Finalized: Archana Reddy, December 31, 2001

TELECONFERENCE MINUTES

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/s/

David T. Lin
12/31/01 02:53:21 PM
I concur.

MEETING MINUTES

Date: November 20, 2001 **Time:** 1:00-2:00 PM **Location:** PKLN; Room 17B-43

NDA: 21-322 **Drug Name:** Luveris™ (lutropin alfa for injection)

Indication: Stimulation of follicular development and ovulation in infertile women with severe deficiency in LH.

Type of Meeting: Status Meeting (7-month)

Sponsor: Serono Laboratories, Inc.

Meeting Chair: Shelley Slaughter, M.D., Ph.D.

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
Shelley Slaughter, M.D., Ph.D. – Medical Team Leader, Division of Reproductive and Urologic Drug Products DRUDP (HFD-580)
Ridgely Bennett, M.D. – Medical Officer, DRUDP (HFD-580)
Eufrecina DeGuia - Regulatory Project Manager, DRUDP (HFD-580)
David Lin, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Dhruba Chatterjee, Ph.D. - Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objectives: To discuss the status of the reviews for this pending NDA.

Background: Luveris™ (lutropin alfa for injection) is indicated for concomitant administration with r-hFSH for the induction of ovulation in infertile women with severe LH deficiency. This drug was investigated clinically under IND 44,108. The NDA was received on May 1, 2001. The primary User Fee goal date for this application is March 1, 2001.

Decisions Reached:
Clinical
- The following dates were agreed upon as due dates for reviews and action package:
  - February 1, 2001 – all reviews should be given to the Clinical Team Leader (reviews should be final)
  - February 15, 2001 – Final Reviews and Action Package should be given to the Division Director
- Office sign off is not required for this NDA
- Medical Reviewer noted that review is still on-going

Chemistry
- review of the application is on-going; facilities inspection will commence at the end of November

Clinical Pharmacology and Biopharmaceutics:
- the reviewer indicated that there is not much clinical pharmacology data to review and will be able to meet the Feb 1st deadline

Statistics
- the reviewer requested the Medical Officer to provide definitions for preferred endpoints

Pharmacology and Toxicology
- review is pending; no issues noted at this time

DSI
- inspection of all four sites were completed; Inspection Summary still pending (per Dr. Connie Lewin, DSI)

Action Items:
- Project Manager will follow up on the status of the Microbiology and OPDRA Tradename reviews

/S/

Signature, minutes preparer

/S/

Concurrence, Chair

cc:
NDA Arch:
HFD-580/Reddy/Rumble
HFD-580/SSlaughters/KMeaker/Bennett/Chatterjee/Lin/Welch/Parekh

Drafted: ed/November 29,2001
Concurrences: tr/December 12, 2001, km/December 11, 2001, dl/December 11, 2001, djc/December 11, 2001, rb/December 11, 2001, ss/December 27, 2001
Finalized: ar/December 31, 2001

MEETING MINUTES

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/s/

Shelley Slaughter
1/2/02 09:50:12 AM
I concur

MEETING MINUTES

Date: December 11, 2001 **Time:** 2:00 – 2:30 PM **Location:** PKLN; Room 17B-43

NDA: 21-322 **Drug Name:** Luveris™ (lutropin alfa for injection)

Indication: Concomitant administration with r-hFSh for the induction of ovulation in infertile women with severe deficiency in LH

Type of Meeting: Status Meeting (8-month)

Sponsor: Serono Laboratories, Inc.

Meeting Chair: Shelley Slaughter, M.D., Ph.D.

Meeting Recorder: Archana Reddy, MPH

FDA Attendees:
Shelley Slaughter, M.D., Ph.D. – Medical Team Leader, Division of Reproductive and Urologic Drug Products DRUDP (HFD-580)
Ridgely Bennett, M.D. – Medical Officer, DRUDP (HFD-580)
Archana Reddy - Regulatory Project Manager, DRUDP (HFD-580)
David Lin, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objectives: To discuss the status of the reviews for this pending NDA.

Background: Luveris™ (lutropin alfa for injection) is indicated for concomitant administration with r-hFSH for the induction of ovulation in infertile women with severe LH deficiency. This drug was investigated clinically under IND 44,108 and included reports of other studies not conducted under an IND and without input from FDA. The NDA was received on May 1, 2001. The primary User Fee goal date for this application is March 1, 2001.

Decisions Reached:
Clinical

- The following dates were agreed upon as due dates for reviews and action package:
  - February 1, 2001 – all reviews should be given to the Clinical Team Leader (reviews due at this time should be final)
  - February 15, 2001 – Final Reviews and Action Package are due to the Division Director
- Medical Reviewer noted that review is still on-going
- Ovulation rate defined based upon mid-luteal progesterone levels
- Pregnancy rates are of concern; pivotal study 21008 showed that the pregnancy rates for the placebo group to be better than 75 IU rhLH in both the group who received hCG and the group who did not receive hCG

Statistics
- the reviewer requested the PM fax questions about the variables in the data sets to the sponsor in the next week

Pharmacology and Toxicology
- review is pending; no issues noted at this time

Microbiology
- review will be completed in a few weeks

Clinical Pharmacology
- review is pending; no issues noted at this time

Chemistry
- review is pending; no approval issues identified at this time
- expiry data could be a potential review issue

DSI
- inspection of all four sites were completed; Inspection Summary still pending (per Dr. Connie Lewin, DSI)

OPDRA Tradename Review
- will be complete in approximately one week

/S/
Signature, minutes preparer

/S/
Concurrence, Chair

cc:
NDA Arch:
HFD-580/Reddy/Rumble
HFD-580/SSlaughters/KMeaker/Bennett/Chatterjee/Lin/Welch/Parekh

Drafted: ar/December 11, 2001
Concurrences: km/December 12, 2001, dl/December 17, 2001, rb/January 3, 2001, ss/January 3, 2001
Finalized: January 3, 2001

MEETING MINUTES

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/s/

Shelley Slaughter
1/8/02 12:40:23 PM
Iconcur

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

5/9/01

NDA 21-322

Serono, Inc.
Attention: Pamela Williamson Joyce
Vice President, U.S. Regulatory Affairs
100 Longwater Circle,
Norwell, MA 02061

Dear Ms. Williamson-Joyce:

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

Name of Drug Product:	Luveris (lutropin alfa for injection) lyophilized, 75 IU
Review Priority Classification:	Standard (S)
Date of Application:	April 30, 2001
Date of Receipt:	May 1, 2001
Our Reference Number:	NDA 21-322

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 30, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be March 1, 2002 and the secondary user fee goal date will be May 1, 2002.

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

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Diane Moore, BS, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Terri F. Rumble
5/9/01 02:52:30 PM

9 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

12-13-01 [illegible]

83 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: June 07, 2001

To: Lisa Mills Regulatory Affairs	**From:** Archana Reddy, MPH Project Manager
Company: Serono Inc.	Division of Reproductive and Urologic Drug Products
Fax number: (781) 878-5001	**Fax number:** 301-827-4267
Phone number: (781) 681-2273	**Phone number:** 301-827-7510

Subject: Request for additional information from the sponsor.

Total no. of pages including cover: 2

Comments:

Lisa,

Please provide a response to the attached requests for NDA 21-322 (Luveris). Thanks.

Archana Reddy

Document to be mailed: ☐ YES ☑ NO

REQUEST FOR ADDITIONAL INFORMATION

NDA: 21-322
Drug Name: Luveris™ (lutropin alfa for injection)
Sponsor: Serono Inc.
Date of Submission: April 30, 2001

Please provide the following information regarding NDA 21-322 (Luveris™) as soon as possible.

CHEMISTRY

(1) Clarify which facility will perform release and stability testing of the drug product.
(2) Are there any light studies conducted on the drug product?
(3) Was L-methionine content measured during stability?
(4) Are there any results from testing change c J during stability?
(5) Will additional drug product stability data be submitted during the review cycle?

OTHER REQUESTS:

(1) Please provide a copy of the approved labeling for this drug product used in European Union countries.

REQUEST FOR ADDITIONAL INFORMATION

NDA: 21-322
Drug Name: Luveris™ (lutropin alfa for injection)
Sponsor: Serono Inc.
Date of Submission: April 30, 2001

Please provide the following information regarding NDA 21-322 (Luveris™) as soon as possible.

CHEMISTRY

(1) Clarify which facility will perform release and stability testing of the drug product.
(2) Are there any light studies conducted on the drug product?
(3) Was L-methionine content measured during stability?
(4) Are there any results from testing change [redacted] during stability?
(5) Will additional drug product stability data be submitted during the review cycle?

OTHER REQUESTS:

(1) Please provide a copy of the approved labeling for this drug product used in European Union countries.

(2) Please provide a new copy of the CD with SAS datasets which was provided in Vol. 1.73. The original CD was not readable. Also, an archival copy of the SAS datasets must be submitted to the electronic document room.

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

/s/

Archana Reddy
6/28/01 09:32:12 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: June 11, 2001

To: Lisa Mills Regulatory Affairs	**From:** Archana Reddy, MPH Project Manager
Company: Serono Inc.	Division of Reproductive and Urologic Drug Products
Fax number: (781) 878-5001	**Fax number:** 301-827-4267
Phone number: (781) 681-2273	**Phone number:** 301-827-7510

Subject: Request for additional information from the sponsor.

Total no. of pages including cover: 2

Comments:

Lisa,

Please provide a response to the attached requests for NDA 21-322 (Luveris). Thanks.

Archana Reddy

Document to be mailed: ☐ YES ☑ NO

CONFIDENTIAL

Serono, Inc.
One Technology Place
Rockland, MA 02370
Tel: 781-982-9000
Fax 781-681-2924
www.seronousa.com

December 21, 2001

Susan Allen, M.D.
Director, Division of Reproductive and Urologic
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 21-322
Luveris™ (lutropin alfa for injection)
Amendment to Pending Application

Dear Dr. Allen,

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001, to a December 14, 2001 Amendment in which updated information on foreign marketing developments was provided, and to an Agency telephone call on December 20, 2001 during which additional information on the product marketed in foreign countries was requested.

As of December 20, 2001, Luveris™ (82.5 IU lutropin alfa, 48 mg sucrose, 0.83 mg dibasic sodium phosphate dihydrate, 0.052 mg monobasic sodium phosphate monohydrate, 0.050 mg polysorbate 20) has received marketing authorization in the following countries:

Country	Marketing Authorization Date
European Union	29 Nov 00
Brazil	06 Sep 01
Iceland	13 Mar 01
Mexico	23 Oct 01
Norway	26 Jul 01
Uruguay	28 Sep 01

Table COM-1 providing the composition of the product marketed in the above-cited countries is attached.

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions, please contact Lisa S. Mills, Manager, Regulatory Affairs, at 781-681-2273 or the undersigned at 781-681-2298.

Yours sincerely,

P.W.J.

Pamela Williamson Joyce
Vice President, US Regulatory Affairs

CONFIDENTIAL

serono

Serono, Inc.
One Technology Place
Rockland, MA 02370 USA
Tel. 781 982 9000
Fax 781 681 2924
www.seronousa.com

December 20, 2001

Susan Allen, M.D.
Director
Division of Reproductive and Urologic Drug Products HFD-580 (Room 17B45)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

DUPLICATE

X1-156-XA

IND 44,108
r-hLH (recombinant human luteinizing hormone)
General Correspondence
Serial No.: 156

Dear Dr. Allen:

Reference is made to IND 44,108 for r-hLH (recombinant human luteinizing hormone) submitted on December 8, 1993.

Effective on January 2, 2002, Serono, Inc. will move its administrative headquarters to the address below. The FAX number has changed, but the telephone numbers have remained the same.

Serono, Inc.
One Technology Place
Rockland, MA 02370 USA
Tel. 781 982 9000
Fax 781 681 2924

The distribution center for Serono's products will not be moved from E J

Please note that Serono, Inc. considers this submission and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions, please contact Lisa S. Mills, Manager, Regulatory Affairs at (781) 681-2273 or the undersigned at (781) 681–2298.

Yours sincerely,

for P.W.J.

Pamela Williamson Joyce
Vice President, Regulatory Affairs

CONFIDENTIAL

serono

DUPLICATE

BB

NDA ORIG AMENDMENT

Serono, Inc.
100 Longwater Circle
Norwell, MA 02061
Tel: 781-982-9000
Fax: 781-878-5001
www.seronousa.com

December 17, 2001

Susan Allen, M.D.
Director, Division of Reproductive and Urologic
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 21-322
Luveris™ (lutropin alfa for injection)
Response to Information Request Letter

Dear Dr. Allen,

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001 and to a December 10, 2001 Agency Information Request Letter in which additional information on the Bioequivalence Study 22372 was requested.

The information requested in the above-cited letter was submitted in NDA 21-322, Volume 44, Pages 025-026 and Pages 033-035. For ease of review, a copy of the December 10, 2001 Agency Information Request Letter is provided in Attachment 1 and a copy of NDA 21-322, Volume 44, Pages 025-26 and Pages 033-035 are provided in Attachment 2. Serono welcomes the opportunity to discuss the requested information in a meeting or teleconference.

Should you have any additional questions regarding the results of Bioequivalence Study 22372, please contact Lisa S. Mills, Manager, Regulatory Affairs at 781-681-2273 to arrange a meeting or teleconference to discuss these results.

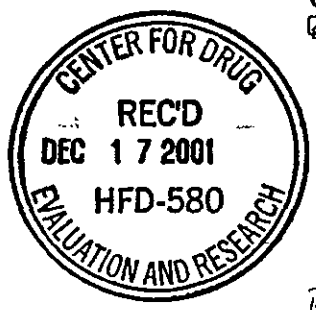
Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Yours sincerely,

Pamela Williamson Joyce
Vice President, US Regulatory Affairs

Document Rec'd
001

ORIGINAL



SERONO, INC.
100 LONGWATER CIRCLE
NORWELL, MA 02061 USA

BM

NDA ORIG AMENDMENT

FACSIMILE TRANSMITTAL SHEET

TO:	FROM:
Archana Reddy Regulatory Project Manager FDA, DRUDP	Lisa S. Mills Serono, Inc.
FAX NUMBER: (301) 827 4267	TELEPHONE NUMBER: (781) 681-2273
PHONE NUMBER: (301) 827 5424	DATE: 14-Dec-01
RE: Luveris NDA 21-322	TOTAL NO. OF PAGES INCLUDING COVER: 35

☐ URGENT ☐ FOR REVIEW ☐ PLEASE COMMENT ☐ PLEASE REPLY ☐ PLEASE RECYCLE

NOTES/COMMENTS:

Dear Archana,

As requested on December 11, 2001, the responses to the Medical Officer's questions are attached.

If you have any questions, please call me at (781) 681 2273.

Sincerely,

Lisa

Lisa S. Mills
Manager, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION

☐ LETTER

CSO INITIALS DATE

CONFIDENTIAL

DUPLICATE

Serono, Inc.
100 Longwater Circle
Norwell, MA 02061
Tel: 781-982-9000
Fax: 781-878-5001
www.seronousa.com

December 14, 2001

Susan Allen, M.D.
Director, Division of Reproductive and Urologic
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

BC
NDA ORIG AMENDMENT

NDA 21-322
Luveris™ (lutropin alfa for injection)
Amendment to Pending Application

Dear Dr. Allen,

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001 and to an Agency telephone call on December 13, 2001 during which updated information on foreign marketing developments was requested.

As of November 30, 2001, Luveris™ has received marketing authorization in the following countries:

Country	Marketing Authorization Date
European Union	29 Nov 00
Brazil	06 Sep 01
Iceland	13 Mar 01
Mexico	23 Oct 01
Norway	26 Jul 01
Uruguay	28 Sep 01

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions about this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, at 781-681-2273 or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President, US Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

12/10/01

NDA 21-322

INFORMATION REQUEST LETTER

Serono, Inc.
Attention: Lisa Mills
Manager, Regulatory Affairs
100 Longwater Circle
Norwell, MA 02061

Dear Ms. Mills:

Please refer to your April 30, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luveris™ (lutropin alfa for injection).

We also refer to your submission dated February 27, 2001, requesting a meeting with the agency to discuss study 22372.

We are reviewing the Biophamaceutical section of your submission and have the following comment and information request. We request a prompt written response in order to continue our evaluation of your NDA.

> The clinically tested formulation and the to-be-marketed formulation differ only in the addition of methionine to the to-be-marketed formulation. The bioequivalence study indicated that all luteinizing hormone C_{max} and AUC parameters were within the regulatory bioequivalence criteria of 80 to 125 %, except the luteinizing hormone $AUC_{0\text{-}last}$. Please provide the clinical argument or justification for the acceptability of 90 % confidence interval of luteinizing hormone $AUC_{0\text{-}last}$ being between [ ] even though the regulatory 90 % confidence interval for bioequivalence criteria is between [ ]. Also, document that the old and new formulations are equally safe and effective via scientific arguments.

If you have any questions, call Archana Reddy, MPH, Regulatory Project Manager, at 301-827-4260.

Sincerely,
{See appended electronic signature page}
Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Terri F. Rumble
12/10/01 05:12:49 PM

CONFIDENTIAL

DUPLICATE

Serono, Inc.
100 Longwater Circle
Norwell, MA 02061
Tel: 781-982-9000
Fax: 781-878-5001
www.seronousa.com

November 26, 2001

David Lin, Ph.D.
Lead Chemist
Division of New Drug Chemistry II, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, Room 17B31
Rockville, MD 20857

NDA ORIG AMENDMENT

N-RSC

NDA 21-322
Luveris™ (lutropin alfa for injection)
Response to FDA Request

Dear Dr. Lin:

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001. Further reference is made to an Agency telephone call on October 24, 2001 during which one sample of Luveris Drug Product was requested.

Please find enclosed one vial of Luveris Drug Product presented in its to-be-marketed container-closure system. This sample is labeled with an investigational drug label since the commercial labeling is not yet available.

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions about this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, at 781-681-2273, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President, US Regulatory Affairs

Cc: Archana Reddy
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

CONFIDENTIAL

DUPLICATE

Serono, Inc.
100 Longwater Circle
Norwell, MA 02061
Tel: 781-982-9000
Fax: 781-878-5001
www.seronousa.com

November 20, 2001

Susan Allen, M.D.
Director, Division of Reproductive and Urologic
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA ORIG AMENDMENT
Novo (BC)

NDA 21-322
Luveris™ (lutropin alfa for injection)
Response to FDA Request for Additional Information

Dear Dr. Allen,

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001 and to an Agency telephone call on November 1, 2001 during which additional information was requested by the Chemistry Team Leader.

Please find enclosed herewith responses to the Agency's request for information.

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

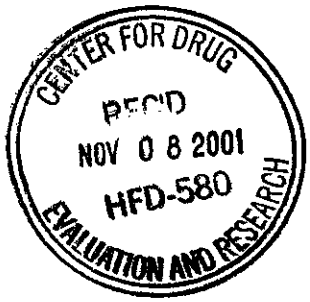
Should you have any concerns about this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, at 781-681-2273, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President, US Regulatory Affairs

CONFIDENTIAL

DUPLICATE



Serono, Inc.
100 Longwater Circle
Norwell, MA 02061
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Fax: 781-878-5001
www.seronousa.com

November 7, 2001

Susan Allen, M.D.
Director, Division of Reproductive and Urology
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

N-51L

NDA 21-322
Luveris™ (lutropin alfa for injection)
Response to FDA Request for Additional Information

Dear Dr. Allen,

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001. Further reference is made to an Agency telephone call on October 24, 2001 during which draft label mock-ups were requested.

Please find enclosed herewith the following draft label mock-ups:

Attachment 1 Vial Label
Attachment 2 Carton
Attachment 3 Carton
Attachment 4 Carton
Attachment 5 Carton

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions about this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, at 781-681-2273, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President, US Regulatory Affairs

CONFIDENTIAL

ORIGINAL

Serono, Inc.

Norwell, MA 02061
Tel: 781-982-9000
Fax: 781-878-5001
www.seronousa.com

October 22, 2001

Susan Allen, M.D.
Director
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA ORIG AMENDMENT

NDA 21-322
Luveris™ (lutropin alfa for injection)
Amendment to Pending Application
Updated Real Time Stability Data

Dear Dr. Allen:

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001.

Please find enclosed herewith updated real time stability information to support an 18 month expiration dating period for Luveris™ Drug Product.

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions, please contact Lisa S. Mills, Manager, Regulatory Affairs at (781) 681-2273 or the undersigned at (781) 681-2298.

Sincerely,

Pamela Williamson Joyce
Vice President, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.L. ☐ MEMO

CSO INITIALS DATE

CONFIDENTIAL

ORIGINAL

NDA ORIG AMENDMENT

Serono, Inc.
100 Longwater Circle
Norwell, MA 02061
Tel. 781 982 9000
Fax 781 878 5001
www.seronousa.com

September 4, 2001

Susan Allen, M.D.
Director, Division of Reproductive and Urology
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 21-322
Luveris™ (lutropin alfa for injection)
Minor Amendment to Pending NDA

Dear Dr. Allen,

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001.

The enclosed minor amendment is being submitted to clarify the difference between the Randomization Order Number and the Randomization ID Number assigned in Serono Study 21008. All randomization assignments were performed in the proper order according to the randomization scheme.

A Randomization ID Number was assigned by the Central Randomization System. This Randomization ID Number represents the unique sequential call number to this System and was recorded on the Case Report Form as the Randomization Number. This number is not necessarily the same as the Randomization Order Number due to aborted calls to the Randomization System, which advanced the call sequence number.

To link the Randomization ID Number to the Randomization Order Number, an additional column has been added to the Randomization Scheme and Codes Table in Appendix 16.1.7 of the report for Study 21008. The revised Appendix 16.1.7 is provided in Attachment 1.

Additionally, the Clinical Site Information binders provided to the Division of Scientific Investigations included both the Randomization Order Number and the Randomization ID Number.

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions about this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, at 781-681-2273, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President, US Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.L. ☐ MEMO

CSO INITIALS DATE

CONFIDENTIAL

ORIGINAL

Serono, Inc.
100 Longwater Circle
Norwell, MA 02061
Tel. 781 982 9000
Fax 781 878 5001
www.seronousa.com

August 30, 2001

Susan Allen, M.D.
Director, Division of Reproductive and Urology
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

N-21-322

NDA 21-322
Luveris™ (lutropin alfa for injection)
120 Day Safety Update Report

Dear Dr. Allen,

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001.

Pursuant to 21CFR314.50(d)(5)(vi)(b), please find enclosed herewith a 120 Day Safety Update Report for Luveris™. The updated report contains data on an additional 491 female patients exposed to Luveris™ during the reporting period (June 30, 2000 – February 28, 2001) over what was submitted in NDA 21-322. There is no change in the safety profile of Luveris™ when administered with follitropin alfa for injection, for stimulation of follicular development in women with severe deficiency in LH .

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, at 781-681-2273, or the undersigned at 781-681-2298.

Yours sincerely,

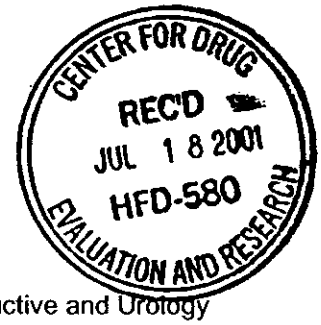
Pamela Williamson Joyce
Vice President, US Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

ORIGINAL CONFIDENTIAL



Serono, Inc.
100 Longwater Circle
Norwell, MA 02061
Tel: 781-982-9000
Fax: 781-878-5001
www.seronousa.com

July 17, 2001

Susan Allen, M.D.
Director, Division of Reproductive and Urology
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

N BC

NDA 21-322
Luveris™ (lutropin alfa for injection)
Minor Amendment to Pending NDA

Dear Dr. Allen,

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001.

Please find enclosed herewith a minor amendment to the above cited pending application. Incorrect pages were erroneously included in the original NDA. The correct pages for the Drug Substance Stability are provided in Attachment 1 and replace pages 197-210B and 215-220 in Volume 8 of NDA 21-322. The corrected information does not change the conclusions regarding the Drug Substance stability.

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, at 781-681-2273, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President, US Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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serono

Serono, Inc.
100 Longwater Circle
Norwell, MA 02061
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www.seronousa.com

580

July 11, 2001

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

RECEIVED
JUL 12 2001
CDR/CDER

M. C

NDA 21-322
Luveris™ (lutropin alfa for injection)
Electronic Regulatory Submission for Archive

Dear Sir / Madam:

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001, to a June 29, 2001 electronic submission, and to a July 5, 2001 Agency telephone call.

As explained in the above cited telephone call, the CD-ROMs provided to the Agency were "unreadable." Please find enclosed herewith additional copies of the CD-ROM which were originally submitted on the June 29, 2001. The enclosed CD-ROMs were generated using Adaptec Easy CD Creator 3.01 with HP CD-Writer Plus 7100 (CD Recorder) and Joliet selected as the File System Type.

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions about this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, at 781-681-2273, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President, US Regulatory Affairs

Enclosure: two duplicate CD-ROMs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ [illegible] ☐ MEMO

CSO INITIALS DATE

Confidential

Serono, Inc.
100 Longwater Circle
Norwell, MA 02061
Tel: 781-982-9000
Fax: 781-878-5001
www.seronousa.com

June 29, 2001

Susan Molchan, M.D.
Division of Scientific Investigations, HFD-46
Food and Drug Administration
7520 Standish Place, Room 125
Rockville, MD 20855

NDA 21-322
Luveris™ (lutropin alfa for injection)
Clinical Site Information for Investigators Participating in Study 21008

Dear Dr. Molchan:

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001 and to an Agency telephone call on June 12, 2001 during which Clinical Site Information was requested.

As requested in the above cited telephone call, please find enclosed herewith individual binders containing Clinical Site Information for each of the following investigators who participated in Study 21008:

- Robert A. Kaufmann, MD – Site 252
- Laurel Stadtmauer, MD, PhD – Site 262
- Thomas Vaughn, MD – Site 254
- Timothy Yeko, MD – Site 253

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions regarding this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, at 781-681-2273, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President, US Regulatory Affairs

CONFIDENTIAL

ORIGINAL

Serono, Inc.
100 Longwater Circle
Norwell, MA 02061
Tel: 781-982-9000
Fax: 781-878-5001
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June 26, 2001

Susan Allen, M.D.
Director, Division of Reproductive and Urology
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA ORIG AMENDMENT

NDA 21-322
Luveris™ (lutropin alfa for injection)
Response to FDA Request for Additional Information

Dear Dr. Allen,

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001 and to an Agency Request for Additional Information dated June 7, 2001.

Please find enclosed herewith responses to the above cited Agency FAX. The Agency comments are presented in **bold** text and the responses provided by Serono are presented in plain text.

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, at 781-681-2273, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President, US Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION

☐ LETTER ☐ N.A.L. ☐ MEMO

CSO INITIALS DATE

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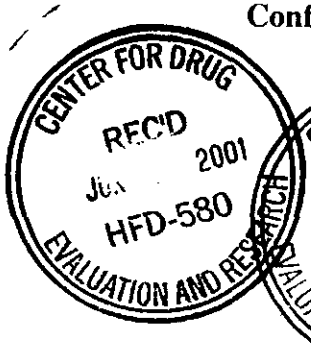

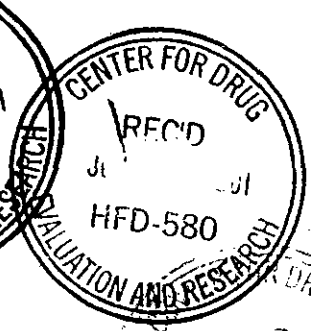

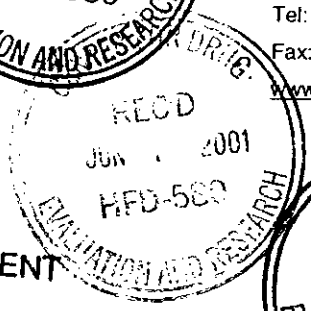

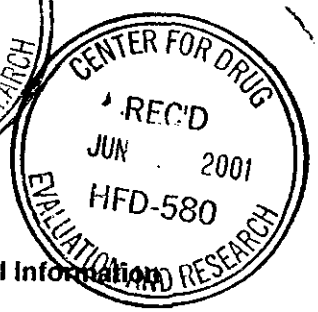

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ORIGINAL

June 12, 2001

Susan Allen, M.D.
Director, Division of Reproductive and Urology
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

NDA 21-322
Luveris™ (lutropin alfa for injection)
Response to FDA Request for Additional Information

Dear Dr. Allen,

Reference is made to Luveris™ NDA 21-322 submitted on April 30, 2001 and to an Agency telephone call on June 7, 2001.

As requested in the above cited telephone call, please find enclosed herewith the following disks:

- CD-ROM containing the SAS datasets as submitted in NDA 21-322, Volume 73 (two copies)
- CD-ROM containing the proposed draft labeling (two copies)

A standard binder containing two copies each of the CD-ROMs has been labeled with "Electronic Regulatory Submission for Archive" for submission to the Electronic Document Room.

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, at 781-681-2273, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President, US Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ [illegible] ☐ MEMO

CSO INITIALS DATE

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April 30, 2001

Susan Allen, M.D.
Director, Division of Reproductive and Urology
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 21-322
Luveris™ (lutropin alfa for injection)
New Drug Application

Dear Dr. Allen,

Reference is made to the pre-IND meeting on May 21, 1992 and to the pre-NDA meeting on December 12, 2001. Further reference is made to a Request for Agency Advice submitted to IND 44,108 (SN-143) on February 27, 2001 and to the response from the Agency dated April 3, 2001.

Pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50 Serono, Inc. herewith submits an original New Drug Application for Luveris™ (lutropin alfa for injection), recombinant-human luteinizing hormone (r-hLH). The Luveris™ NDA has been pre-assigned the number NDA 21-322.

User Fee number 4034 was assigned. Under section 736(a)(1)(E) of the FD&C Act, this original New Drug Application (NDA) is not subject to an application fee since Luveris™ is indicated for a rare disease or condition designated under section 526 of the FD&C Act (orphan drug designation).

On October 7, 1994, Luveris™ was granted orphan-drug designation (application number — for the indication that is the subject of this NDA. A copy of the designation letter from the Office of Orphan Product Development is provided in Volume 1, page 079.

Chemistry, Manufacturing, and Controls Overview

Luveris™ is a pharmaceutical preparation of human luteinizing hormone of recombinant origin. Luteinizing hormone (LH) is a heterodimeric glycoprotein from the same family as the pituitary gonadotropins (human follicle stimulating hormone, human chorionic gonadotropin) and human thyroid stimulating hormone. It consists of two non-covalently linked subunits (designated α and β) of 92 and 121 amino acids, respectively.

Lutropin alfa is produced by recombinant DNA technology and is formulated for use by subcutaneous injection. The drug product is available as a lyophilized powder in vials containing 82.5 IU lutropin alfa for injection with accompanying diluent for a deliverable dose of 75 IU.

New Formulation and Bioequivalence

Bioequivalence Study 22372 was conducted for the purpose of comparing the bioavailability of the drug product formulation administered in clinical trials and the "to-be-marketed" formulation, which contains the additional excipient, methionine. Agency advice on the results of this bioequivalence study was requested on February 27, 2001 and received on April 3, 2001. The information requested by the Agency is located in Volume 44, page 033.

Proposed Indication

Luveris™ (lutropin alfa for injection) is indicated for concomitant administration with r-hFSH for the induction of ovulation in infertile women with severe LH — deficiency.

Clinical Overview

Luveris™ was investigated clinically under IND 44,108 submitted on December 8, 1993. As of the data cut-off for this application, Serono has completed the clinical phase and data analysis of five

controlled clinical trials of Luveris™. These studies, which are described below, were conducted under the principles of Good Clinical Practice (GCP) in the United States and in Europe and Israel.

Study 6253 is entitled "An open label, randomized, dose-finding, multicenter, pivotal study to determine the minimal effective dose and to assess the safety of recombinant human Luteinizing Hormone (r-hLH) to support recombinant human Follicle Stimulating Hormone (r-hFSH) induced follicular development in LH and FSH deficient anovulatory women (WHO Group I)." The objectives of the study were to assess the need for and efficacy of r-hLH for inducing ovulation in WHO Group I anovulation; to determine the minimal effective dose of r-hLH to be administered during r-hFSH stimulation of follicular development; and to assess the safety of r-hLH administered subcutaneously to women for up to 20 days at a dose of up to 225 IU/day.

This study demonstrated the efficacy of r-hLH for supporting FSH-induced follicular development prior to triggering ovulation in anovulatory women. A daily dose of 75 IU r-hLH was effective in the majority of anovulatory women.

Study 21008 is entitled "A phase III, prospective, randomized, controlled, double-blind, multicenter study to confirm the efficacy and safety of recombinant human Luteinizing Hormone (r-hLH), 75 IU, administered subcutaneously, to support recombinant human Follicle Stimulating Hormone (r-hFSH)-induced follicular development in women with hypogonadotropic hypogonadism and severe LH deficiency who desire pregnancy." The study was designed to confirm the efficacy and safety of the 75 IU dose of r-hLH co-administered with 150 IU r-hFSH for induction of follicular development in women with hypogonadotropic hypogonadism (HH) and profound LH deficiency (LH <1.2 IU/L) who desired pregnancy.

The data of Study 21008 confirm the findings of Study 6253 on the efficacy, safety and suitability of r-hLH co-administered with r-hFSH for induction of follicular development and ovulation in infertile women with severe LH and FSH deficiency. These data are further consistent with the literature reporting the effects of LH in this population in this indication.

Study 6905 is entitled "An open, randomized, dose finding, multicenter study to determine the minimal effective dose and to assess the safety of r-hLH to support r-hFSH induced follicular development in anovulatory women with hypogonadotropic hypogonadism." The study objectives were to assess the need for and efficacy of r-hLH for inducing ovulation in women with hypogonadotropic hypogonadism; to determine the minimal effective dose of r-hLH to be administered during r-hFSH stimulation of follicular development; and to assess the safety of r-hLH administered SC to women for up to 21 days per cycle for a maximum of three cycles at a dose of up to 225 IU/day.

Study 6905 addressed the efficacy of r-hLH in a broadly based population of anovulatory women with hypogonadotropic hypogonadism. The study results demonstrated that r-hLH is well-tolerated and, when co-administered with r-hFSH, presents a similar profile of safety to r-hFSH alone. In this population, a dose response to concomitant administration of r-hLH and r-hFSH was not demonstrated, other than in the subset of women with severe LH and FSH deficiency.

Study 7798 is entitled "A phase III multicenter study for the evaluation of the efficacy and safety of recombinant human Luteinizing Hormone (r-hLH) to support recombinant human Follicle Stimulating Hormone (r-hFSH)-induced follicular development in LH and FSH deficient anovulatory women (WHO group I)." The objectives of this study were to assess the need for and efficacy of r-hLH in WHO Group I anovulatory women to support follicular development and induce ovulation and to evaluate the safety of r-hLH administered subcutaneously.

This study confirms a benefit of co-administration of r-hLH with r-hFSH in hypogonadotropic patients with severe gonadotropin deficiency.

Study 8297 is entitled "A phase III multicenter, non-comparative study to evaluate the efficacy and safety of recombinant human Luteinizing Hormone (r-hLH) to support recombinant human Follicle Stimulating Hormone (r-hFSH)-induced follicular development in LH and FSH deficient anovulatory women (WHO Group I)." The objectives of this study were to assess the efficacy of r-hLH associated

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with r-hFSH in WHO Group I anovulatory women to support follicular development and induce ovulation.

The results of this study confirm the efficacy and safety of r-hLH to support r-hFSH induced follicular development and luteinization in anovulatory women with hypogonadotropic hypogonadism.

Submission Content

The NDA consists of 93 volumes and is allocated as follows:

Volume 1:	Cover letter, FDA Form 356h (Application Form), FDA Form 3397 (User Fee Cover Sheet), Item 13 (Patent Information), Item 14 (Patent Certification), Item 16 (Debarment Certification), Item 17 (Field Copy Certification), Item 18 (User Fee Waiver), Item 19 (FDA Form 3454 Financial Disclosure), Item 20 (Statement of Market Exclusivity Pediatric Use Waiver), Item 1 (Overall NDA Index), Item 2 (Draft Labeling)
Volume 2:	Item 3 – Application Summary
Volumes 3-14:	Item 4 – Chemistry, Manufacturing, and Controls Information
Volumes 15-43:	Item 5 – Nonclinical Pharmacology and Toxicology
Volumes 44-53:	Item 6 – Human Pharmacokinetics and Bioavailability
Volume 54:	Item 7 – Microbiology (Sterility Assurance)*
Volumes 55-72:	Item 8 – Clinical Data
Volumes 73-86:	Item 10 – Statistical Methodology
Volumes 87-91:	Item 11 – Case Report Tabulations
Volumes 92-93:	Item 12 – Case Report Forms

*Please note that the product is produced by [redacted]. The summary of the validation of [redacted] is contained in Item 7.

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, at 781-681-2273, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President, US Regulatory Affairs

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February 27, 2001

Susan Allen, M.D.
Director
Division of Reproductive and Urologic Drug
Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-322
Luveris™ (lutropin alfa for injection)
Request for Meeting: Type C

Dear Dr. Allen:

Reference is made to Serono's planned New Drug Application (NDA) 21-322 for Luveris™ (lutropin alfa for injection) and to a pre-NDA meeting on December 12, 2000.

Pursuant to 21 CFR 312.47(a), please find enclosed herewith a request for a meeting (Type C) with the Agency. Serono would appreciate scheduling of the meeting as soon as possible (approximately one hour in duration). Please note that this Request for a Type C meeting replaces Serono's request for a Type A meeting submitted to the Agency on February 23, 2001.

Please note that Serono, Inc. considers this submission and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions concerning this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, or the undersigned at (781) 982-9000.

Sincerely,

Pamela Williamson Joyce
Vice President, Regulatory Affairs

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February 23, 2001

Susan Allen, M.D.
Director
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-322
Luveris™ (lutropin alfa for injection)
Request for Meeting: Type A

Dear Dr. Allen:

Reference is made to Serono's planned New Drug Application (NDA) 21-322 for Luveris™ (lutropin alfa for injection) and to a pre-NDA meeting on December 12, 2000. Reference is also made to IND 44,108 for recombinant human luteinizing hormone (lutropin alfa for injection) submitted on December 8, 1993.

Pursuant to 21 CFR 312.47(a), please find enclosed herewith a request for a meeting (Type A) with the Agency. Serono would appreciate scheduling of the meeting as soon as possible (approximately one hour in duration) and proposes the following dates for consideration: March 1, 2, 5, 6, 2001 or other date to be mutually agreed.

Please note that Serono, Inc. considers this submission and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions concerning this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, or the undersigned at (781) 982-9000.

Sincerely,

Pamela Williamson Joyce
Vice President, Regulatory Affairs

MEETING MINUTES

Date: December 12, 2000 **Time:** 1:30-2:30 PM **Location:** PKLN; Conference Room "L"

NDA: 21-322 **Drug Name:** Luveris™ (lutropin alfa for injection)

Indication: Stimulation of follicular development and ovulation in infertile women with severe deficiency in LH

Type of Meeting: Pre-NDA meeting

Sponsor: Serono Laboratories, Inc. **External Participant Lead**: Pamela Williamson Joyce

Meeting Chair: Dr. Susan Allen

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
Susan Allen, M.D., M.P.H. - Director, Division of Reproductive and Urologic Drug Product DRUDP (HFD-580)
Daniel Shames, M.D. – Deputy Director, DRUDP (HFD-580)
Terri Rumble - Chief, Project Management Staff, DRUDP (HFD-580)
Eufrecina DeGuia - Regulatory Project Manager, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Duu-Gong Wu, Ph.D.- Chemistry Reviewer, DNDC II @ Division of Metabolic and Endocrine Drug Products; DMEDP (HFD-510)
Johnny Lau, Ph.D. - Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Shelley Slaughter, M.D., Ph.D., Medical Team Leader, DRUDP (HFD-580)
David Lin, Ph.D. – Chemistry Reviewer, DRUDP (HFD-580)
Yvonne Yang, Ph.D. – Chemistry Reviewer, DMEDP (HFD-510)

External Participants:
Serono Laboratories, Norwell, MA.
Thomas Lang - Sr. Vice President, Strategic Product Development
Pamela Williamson Joyce – Vice President, Regulatory Affairs
Louis O'Dea, M.D. – Vice President, Clinical Development, Regional Medical Director
Fanny O'Brien – Principal Biostatistician
Lisa Mills – Manager, Regulatory Affairs

Ares Serono Geneva, Switzerland
Ernest Loumaye, M.D. – Chief Medical Director, Vice President, Clinical Development
Lindsay Ham – Director, Worldwide Regulatory Affairs
Reinoud Dreibergen – Director, Centre of Expertise, Quality Control Systems
Robert Bassett – Manufacturing Product Director, Reproductive Health

Meeting Objectives: To determine whether the clinical data package (efficacy and safety data from the Phase 3 studies), Chemistry, Manufacturing and Controls information, and format are sufficient to support filing of an NDA submission.

Background: The reference IND for this application is IND 44,108 (previously known as Lhadi). After some discussions and guidance from the Division on the development of lutropin alfa, the sponsor has performed an additional Phase 3 study (Study 21008) to assess its efficacy and safety in women with profound gonadotropin deficiency. This confirmatory study of the proposed 75 IU dose will comprise the pivotal data for the NDA submission. Serono anticipates submitting the NDA in February 2001.

Decisions Reached:

Clinical

Question #1:

Following discussions with the FDA, Serono has completed a double-blind, placebo-controlled, randomized study to confirm efficacy of LH, co-administered with FSH, for induction of follicular development and ovulation in infertile women with severe LH and FSH deficiency. The data of this study confirm the statistical and clinical efficacy of r-hLH in this indication.

- Does the FDA concur that these additional new data and the study data integration strategy for the ISE and ISS are adequate for the filing of r-hLH in this indication?
- Does the FDA have any suggestions on the format and presentation of these clinical data?

Answer:

- the Division acknowledges that the sponsor conducted the double-blind placebo (FSH alone)-controlled study that the Division had requested and this would be considered favorably; however, the fileability of the NDA will be determined after the NDA is submitted
- the sponsor can follow their study integration strategy; however, the data should also be analyzed separately for each of the studies submitted in support of the indication; the analysis should be stratified by LH levels according to the various LH screening values used in the studies to be submitted, for example LH levels < 1.2 IU/L, 1.2-5 IU/L, 5-9 IU/L and 9-13 IU/L.

Chemistry

Question #1:

Serono has initiated a modification to the formulation of r-hLH by the addition of methionine [ ] in the to-be-marketed product. The manufacturing process has been qualified with this new formulation. Additionally, a bioequivalence study is currently being performed to confirm pharmacokinetic identity of the two formulations (with and without methionine).

- Does FDA concur that the plan is acceptable for support of registration?

Answer:

- the sponsor's approach is acceptable; since the new formulation has methionine, the methionine content must be monitored and reported in the NDA
- stability study should monitor methionine content
- fileability determination will be made at the time of submission

Question #2:

Serono's position is that the chemistry, manufacturing and controls information are sufficient for filing and subsequent approval of the NDA.

- Does the FDA have any recommendations or comments on the content, format and presentation of these CMC data?

Answer:

- sponsor was asked to follow guidelines for CBER Biotechnology Products
- fileability will be determined at the time of the NDA submission and subsequent approvability will be determined after a thorough review of the application

Clinical Pharmacology and Biopharmaceutics Comments and Recommendations

For Study 22372:

a. Please include complete bioanalytical report to quantitate serum r-hLH concentrations (individual subject values, specificity, cross-reactivity (if any), lower limit of quantitation, inter- and intra- day assay precision, accuracy, linearity and validation information), which should accompany the final study report.
b. Quantitate the actual subcutaneous (SC) r-hLH dose administered as compared to the nominal dose.
c. Report the SC site of injections for the clinical safety and efficacy studies as well as the SC site of injection for this study.
d. Note that the regulatory bioequivalence criteria are that the 90% confidence intervals for the point estimate of the geometric test/reference mean rations for drug C_{max} and AUC should fall within 80 – 125%.

The following should be provided for the NDA:

a. Rationale for dose selection in Section 6
b. Final report for Study 22372
c. Study Synopsis for Study 22372
d. Pharmacokinetic data for Study 22372 in electronic diskettes (ASCII format) with user guide as well as study reports and Section 6 summary (if possible)

Statistics

- the format is acceptable

Action Items:

- meeting minutes will be sent to the sponsor within 30 days

Signature, minutes preparer

Concurrence, Chair

NOTE: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcome.

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November 13, 2000

Susan Allen, M.D.
Director
Division of Reproductive and Urologic Drug
Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-322
Luveris™ (lutropin alfa for injection)
Information Package for Pre-NDA Meeting (Type B)

Dear Dr. Allen:

Reference is made to Serono's planned New Drug Application (NDA) 21-322 for Luveris™ (lutropin alfa for injection). Reference is also made to IND 44,108 for recombinant human luteinizing hormone (lutropin alfa for injection) submitted on December 8, 1993.

Please find enclosed a pre-NDA Meeting Information Package (15 copies) for Luveris™ (lutropin alfa for injection) containing a summary of the Phase III Clinical Data and Chemistry, Manufacturing, and Controls information. The meeting is scheduled for:

Date:	December 12, 2000
Time:	1:30 pm to 3:00 pm
Subject:	Pre-NDA Meeting (Type B)
Place:	to be determined

Please note that Serono, Inc. considers this submission and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions concerning this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, or the undersigned at (781) 982-9000.

Sincerely,

Pamela Williamson Joyce
Vice President, Regulatory Affairs

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October 27, 2000

Susan Allen, M.D.
Director
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-322
Luveris™ (lutropin alfa for injection)
Request for Meeting: Pre-NDA (Type B)

Dear Dr. Allen:

Reference is made to Serono's planned New Drug Application (NDA) 21-322 for Luveris™ (lutropin alfa for injection). Reference is also made to IND 44,108 for recombinant human luteinizing hormone (lutropin alfa for injection) submitted on December 8, 1993.

Pursuant to 21 CFR 312.47(b)(2), please find enclosed herewith a request for a pre-NDA Meeting (Type B).

Please note that Serono, Inc. considers this submission and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions concerning this submission, please contact Lisa S. Mills, Manager, Regulatory Affairs, or the undersigned at (781) 982-9000.

Sincerely,

Pamela Williamson Joyce
Vice President, Regulatory Affairs

Minutes of Teleconference

Date: May 3, 1999 **Time:** 10:30-11:00 AM **Location:** Parklawn; 17B43

IND 44,108 **Drug Name:** Luadi (recombinant Luteinizing Hormone [r-hLH]

Indication: Treatment of Idiopathic Hypogonadotropic Hypogonadism (IHH)

External Participant: Serono

Type of Meeting: Guidance

Meeting Chair: Dr. Marianne Mann **External Participant Lead:** Mr. Dennis Bucceri

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products DRUDP; (HFD-580)
Shelley Slaughter, M.D., Ph.D., Acting Team Leader, DRUDP (HFD-580)
Ridgely Bennett, M.D., M.P.H., Medical Officer, DRUDP (HFD-580)
Terri Rumble, B.S. N., Chief Project Management Staff, DRUDP (HFD-580)
Diane Moore, Regulatory Project Manager, DRUDP (HFD-580)
Eufrecina DeGuia, Regulatory Project Manager, DRUDP (HFD-580)
Kate Meaker, M.S., Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

External Constituents:
Dennis Bucceri, R.Ph., Executive Director, Regulatory Affairs, Serono Laboratories
Louis O'Dea, M.D., Executive Medical Director, Reproductive, Endocrinology and Growth
Karen Currie, Medical Research Specialist, Serono Laboratories
Fanny O'Brien, Ph.D., Senior Statistician, Serono Laboratories
James Breitmeyer, M.D., Senior Vice President, Research Serono Laboratories
Susan Kenley, Ph.D., Director, Biometrics Serono Laboratories
Debbie DeMuria, Pharm. D., Senior Regulatory Associate, Serono Laboratories
Ernest Loumaye, M.D., Vice President, Corporate Development
Lindsay Ham, Ph.D., Manager, Corporate Regulatory Affairs

Meeting Objectives: To convey comments to the sponsor regarding the trial design of their proposed confirmatory clinical study, Protocol #IMP21008, submitted on March 22, 1999.

Background: Luadi is being developed as an orphan drug for the treatment of Idiopathic Hypogonadotropic Hypogonadism (IHH). It was agreed in the teleconference held on February 23, 1999, that an additional clinical study would be necessary to obtain an adequate database for filing an NDA for Luadi. The sponsor submitted the protocol on March 22, 1999.

Discussion Points:

- the sponsor wishes to study a population with LH level < 1.2 IU; although the Division prefers that the study population includs patients with higher LH levels, it was agreed that the study could proceed, but the sponsor was reminded that the label would reflect negative results from patients with levels of LH <5.0 IU but >1.2 IU
- single-dose study of 75 IU can be conducted with the caveat that the NDA application will be carefully reviewed regarding all dosage levels; safety of 25 IU vs. 75 IU doses in the patient population will be compared, and if the 25 IU is effective it could lead to a possible review issue given that the lowest effective dose was not studied
- the use of placebo arm consisting of nine additional subjects with concurrent data, not historical data is recommended; this would be considered the pivotal study
- both the ultrasonographer and patient should be blinded
- since the primary endpoint is a combination of follicular development and mid-luteal progesterone levels, a more stringent cut-off of 10 ng/mL for progesterone level should be considered as a better indicator of follicular development instead of the proposed 7.8 ng/mL cut-off
- the 200 pg/mL is a more acceptable E_2 level as an indicator of follicular development than the proposed 109 pg/mL E_2 level

Decisions reached:

- sponsor will attempt to blind the study as much as possible and re-submit the protocol
- the E_2 and progesterone levels will be reevaluated and a valid argument for the proposed levels will be submitted for review
- the progesterone upper limit will be 10 ng/mL
- the estimated success rate should be recalculated for each treatment group using the new criteria since the P_4 level (and possible E_2 level) used to determine the treatment success may change
- the sample size for the pivotal study reflecting the revised estimates of anticipated success rates and the addition of a placebo arm should also be recalculated

Post-meeting Addendum:

- a phone call was made to the sponsor requesting them to submit a justification or rationale as to why blinding is so difficult for this study in the revised protocol

Ellen Gin
Signature, minutes preparer

Maria Man, M.D.
Concurrence, Chair
5/24/99

MEETING MINUTES

Date: November 30, 1998 **Time:** 4:30 - 6:00 PM **Location:** Parklawn; Conference Room "C"

IND: 44,108 **Drug Name:** LHadi ([recombinant human Luteinizing Hormone (r-hLH)]

External Participant: Serono Laboratories, Inc. **Indication:** Hypogonadotropic Hypogonadism

Type of Meeting: Guidance

Meeting Chair: Dr. Lisa Rarick **External Participant Lead:** Mr. Thomas Lange

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Florence Houn, M.D., M.P.H. - Deputy Director, Office of Drug Evaluation II (ODE II; HFD-102)
Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Marianne Mann, M.D. - Deputy Director, DRUDP (HFD-580)
Ridgely Bennett, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Lana L. Pauls, M.P.H. – Acting Associate Director, DRUDP (HFD-580)
Diane Moore - Project Manager, DRUDP (HFD-580)
Terri Rumble – Acting, Chief, Project Management Staff, DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
John McCormick, M.D. – Deputy Director, Office of Orphan Drug Development (HF-35)

External Constituents:
Karen Currie - Medical Research Specialist, Serono
Debbie DeMuria, Pharm. D., - Senior Regulatory Associate, Serono
Lindsay Ham - Manager, Corporate Regulatory Affairs, Serono
Susan Kenley, Ph.D. - Biometrics, Serono
Thomas A. Lang - Senior Vice President, Regulatory Affairs, Serono
Ernest Loumaye, M.D. - Vice President, Corporate Clinical Development, Serono
Fanny O'Brien Ph.D. – Senior Statistician, Serono
Louis O'Dea, M.B., B.Ch., B.A.O., F.R.C. (C) - Executive Medical Director, Reproductive Endocrinology, Serono
Hisham Samra, M.D. – President, Serono Laboratories, Inc., Serono
– Consultant, [redacted]
[redacted] – Statistical Consultant, [redacted]

Meeting Objectives:
To discuss the fileability of LHadi.

Background:
The original briefing document was submitted on June 15, 1998. Teleconferences were held on June 30 and July 10, 1998, between the Agency and Serono to discuss the filoability of an NDA for LHadi. An additional briefing document was submitted on July 27, and a summary of clinical information previously

submitted in the pre-NDA meeting packages was submitted on September 4, 1998. On November 18, 1998, the sponsor submitted a request to meet with Dr. Lumpkin and representatives from the Office of Orphan Drug Development and the Office of Women's Health.

Discussion Points: (see attached)

- FDA Issues
  - the sponsor is maintaining Orphan status for this indication
  - the sponsor now seeks to submit the European trial (6253) as the pivotal trial with three supportive studies from three different countries in support of an NDA; when the original protocols were submitted, neither the US nor the European study was designated as pivotal; they were to be identical studies treated with equal weight
  - at the Pre-IND meeting held on May 21, 1992, the development plan was discussed; two studies, using the same protocol, were proposed, one in Europe and one in the USA
  - when the IND was submitted, only the protocol for the U.S. Study (6905) was included
  - in July 1994, a protocol amendment was submitted with significant changes in the US protocol prior to initiation of the study
  - the European study is significantly different from the US study
  - on Nov 18, 1998, new data from the Spanish study was submitted using moderately LH deficient patients
  - 15 patients were studied in a German study; there were six pregnancies in the 75 IU/L group, one in the 150 IU group, and one in the 225 IU dose group
  - if efficacy is dose related, the fewer number of pregnancies in the higher dose group should be explained
- Sponsor's Views to FDA Issues
  - the 75 IU/L dose was chosen by the sponsor as the optimal dose for efficacy and safety
  - originally, both the US and European study protocols were identical, but the US study had enrollment problems which forced them to change the protocol
- Statistics Issues
  - the trend test is proposed as a confirmatory statistical tool for efficacy assessment
  - step-down doses were studied, beginning with the highest dose, to show significance in order to avoid multiple-comparison doses and head-to head comparisons at lower alpha levels
  - FDA considers these trend tests to be exploratory tests and not significant for a pivotal trial
  - the US and European studies were designed as dose-finding studies and no hypothesis was set for the studies at the outset; additionally, exploratory analyses were used to detect significance
  - this data can be used to make exploratory conclusions for further research; however, making efficacy conclusions based on these analyses is problematic
  - the analysis was a post-hoc comparison; no NDA has been approved using only one study analyzed using a trend test
  - these studies were not powered on any criteria other than the limited size of the patient population
  - the best overall result in the US study was with the 25 IU/L and low LH group, both in the overall study and in the "low LH" subset

Decisions reached:

- review issues will be discussed at the Office level
- the sponsor should submit a justification for the trend test analysis
- If filed, the application may be taken to an Advisory Committee
- a justification for the analyses can be sent after the fileability issue has been resolved

- the sponsor should clarify which studies will be used to support the NDA submission; any future approaches and plans should be submitted
- the German and Spanish study data should be submitted for review; the data will be available in April 1999
- the sponsor plans to submit the NDA in April 1999

Action Items:

Item:	Responsible Person:	Due
• submit data from German and Spanish studies	Serono	April, 1999
• forward discussion items to Office Level	Dr. Rarick	one month
• communicate Office response to sponsor	Ms. Moore	upon receipt

Diane Moore 1/12/99
Signature, minutes preparer

Signature, Chair

TELECONFERENCE MINUTES

Date: July 10, 1998 **Time:** 1:30 - 2:15 PM **Location:** Parklawn; Room 17B-43

IND: 44,108 **Drug Name:** Lhadi [Recombinant Human Luteinizing Hormone(r-hLH)]

External Participant: Serono Laboratories, Inc. **External Participant Lead:** Mr. Thomas Lange

Type of Meeting: Pre-NDA

Meeting Chair: Lisa Rarick, M.D.

Meeting Recorder: Alvis Dunson

FDA Attendees:

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Marianne Mann, M.D. - Deputy Director, DRUDP (HFD-580)
Ridgely Bennett, M.D. - Medical Officer, DRUDP (HFD-580)
Shelley Slaughter, M.D., Ph.D. - Medical Officer, DRUDP (HFD-580)
Kate Meaker, M.S. - Mathematical Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Alvis Dunson - Project Manager, DRUDP (HFD-580)

External Constituents:

Thomas Lange - Regulatory Affairs
Lisa Mills - Regulatory Affairs
Louis O'Dea - Clinical Director
Susan Kinley - Statistics
Karen Currie - Clinical Research
Eduardo Kelley - Medical Director
Fanny O'Brien - Statistics
[redacted] - Statistics Consultant
Lindsay Ham - Corporate Regulatory Affairs

Meeting Objectives:

To discuss the clinical section of a planned NDA submission.

Discussion Points:

- Studies 6253 and 6905 were designed as dose-finding studies and appear adequate as such, however, a pivotal study should be conducted using this selected dose to demonstrate efficacy by comparing Gonal-F alone with Gonal-F plus rhLH

- an "evaluable" subset analysis of data in Studies 6253 and 6905 is acceptable if a discussion of any differences between this analysis and an intent-to-treat (ITT) analysis is presented; an ITT analysis will be the primary focus for the NDA

- the subset analyses and pooled analyses already submitted will be considered secondary/exploratory for the NDA

- the benefit of LHadi® in LH-deficient women should be further defined

- the number of pregnancies achieved in Study 6905 in which the 1.2 IU/L dose was given should be submitted; an explanation of how many of the 14 subjects who achieved pregnancy had a screening LH of <1.2 IU/L should be submitted

- the exclusion of the three untreated patients in Study 6905 is acceptable

Unresolved Issues: None

Action Items:

Item:	**Responsible Person:**	**Due Date:**
♦ further define benefit of LHadi® in LH-deficient women	Serono Labs	?
♦ submission of pregnancy data in Study 6905	Serono Labs	?
♦ submission of ITT analysis for Studies 6253 and 6905	Serono Labs	?

8/4/98
Signature, minutes preparer

8/4/98
Concurrence, Chair

drafted: ADunson/7.20.98/i44108.im

cc:
NDA Arch:
HFD-580
HFD-580/JMercier/Attendees
HFD-580/ADunson/7.20.98

Concurrences:
RBennett, MMann7.21.98/LRarick7.22.98/LPauls7.24.98/KMeaker7.27.98

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development(HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

October 7, 1994

Serono Laboratories, Inc.
Attention: Ms. Marlene Booth
Vice President, Regulatory Affairs and Quality Assurance
100 Longwater Circle
Norwell, MA 02061

Dear Ms. Booth:

Reference is made to your orphan drug application of January 12, 1994 submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act for the designation of recombinant human luteinizing hormone (r-hLH) as an orphan drug (application [ ]). We also refer to your amendments dated June 14 and September 14, 1994.

We have completed the review of this application, as amended, and have determined that recombinant human luteinizing hormone qualifies for orphan designation for use in association with recombinant human follicle stimulating hormone for the treatment of women with chronic anovulation due to hypogonadotropic hypogonadism. Please note that it is recombinant human luteinizing hormone and not its formulation that has received orphan designation.

Prior to marketing approval, sponsors of designated orphan products are requested to submit written notification to this Office of their intention to exercise orphan drug exclusivity if they are the first sponsor to obtain such approval for the drug. This notification will assist FDA in assuring that approval for the marketing of the same drug is not granted to another firm for the statutory period of exclusivity. Also please be advised that if recombinant human luteinizing hormone were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA. Therefore, prior to final marketing approval, sponsors of designated orphan products are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

In addition, please inform this office annually as to the status of the development program, and at such time as a marketing application is submitted to the FDA for the use of recombinant human luteinizing hormone as designated. If you need further assistance in the development of your product for marketing, please feel free to contact Mr. Peter Vaccari at (301) 443-4718.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

Sincerely yours,

Marlene E. Haffner, M.D., M.P.H.
Director

65 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling