CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-522/S-013

ADMINISTRATIVE DOCUMENTS

13. PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG

21 U.S.C. 355 (b): The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use or sale of the drug.

Nutropin AQ® [somatropin (rDNA origin) injection] falls within the scope of the claims of Patent Number 5,763,394. This patent will expire on June 9, 2015. A copy of the patent is included in this section.

US005763394A

United States Patent [19]

O'Connor et al.

[11] Patent Number: 5,763,394

[45] Date of Patent: Jun. 9, 1998

[54] **HUMAN GROWTH HORMONE AQUEOUS FORMULATION**

[75] Inventors: **Barbara H. O'Connor**, San Carlos; **James Q. Oesterein**, Moss Beach, both of Calif.

[73] Assignee: **Genentech, Inc.**, South San Francisco, Calif.

[21] Appl. No.: 117,156

[22] PCT Filed: Jul. 29, 1993

[86] PCT No.: PCT/US93/07149

§ 371 Date: Sep. 14, 1993

§ 102(e) Date: Sep. 14, 1993

[87] PCT Pub. No.: WO94/03198

PCT Pub. Date: Feb. 17, 1994

Related U.S. Application Data

[63] Continuation of Ser. No. 923,401, Jul. 31, 1992, abandoned, which is a continuation-in-part of Ser. No. 751,424, Aug. 28, 1991, abandoned, which is a continuation of Ser. No. 182,262, Apr. 15, 1988, Pat. No. 5,096,885.

[51] Int. Cl.[6] A61K 38/27; C07K 14/61

[52] U.S. Cl. 514/12; 530/324

[58] Field of Search 514/12

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,929,137	12/1975	Moore et al.
4,297,344	10/1981	Schwarz et al.
4,333,920	11/1982	Chan et al.
4,621,717	11/1986	Fernandes et al.
4,789,441	11/1988	Thurow .
4,812,557	3/1989	Yasuda et al.
4,815,568	3/1989	Hamilton, Jr. et al.
4,852,536	8/1989	Tyle
4,917,685	4/1990	Viswanatham et al.
5,005,264	4/1991	Miller et al. .
5,096,885	3/1992	Pearlman et al. .
5,225,324	6/1992	Clark et al.
5,282,258	1/1993	Chou .
5,317,017	5/1994	Kudsk .
5,374,620	12/1994	Clark et al.
5,567,677	10/1996	Castaneda et al.
5,597,802	1/1997	Clark et al.

FOREIGN PATENT DOCUMENTS

A-30771/89	9/1989	Australia .
AUA30771/8	9/1989	Australia
164598	4/1980	Denmark
0 131 864	1/1985	European Pat. Off
0 193 917	9/1986	European Pat. Off
0 211 601	2/1987	European Pat. Off
0211601	2/1987	European Pat. Off
0 303 746	2/1989	European Pat. Off.
0303746	2/1989	European Pat. Off
0 400 856	1/1991	European Pat. Off
0 433 113	6/1991	European Pat. Off .
72389	7/1984	Israel
1-502835	12/1989	Japan .
8909613	10/1989	WIPO
WO89/09613	10/1989	WIPO
WO91/15509	10/1991	WIPO
WO91/18621	12/1991	WIPO
WO92/17209	10/1992	WIPO
WO93/00109	1/1993	WIPO
WO93/12811	7/1993	WIPO
WO93/19776	10/1993	WIPO
WO93/22335	11/1993	WIPO
WO94/03198	2/1994	WIPO .

OTHER PUBLICATIONS

Skottner et al., "Growth Responses in a Mutant Dwarf Rat to Human Growth Hormone and Recombinant Human Insulin-Like Growth Factor I" *Endocrinology* 124 (5): 2519–2526 (1989).

Becker, et al., *Biotechnology & Applied Biochemistry* 9:478–487 (1987).

Pearlman, et al., *Current Communications in Molecular Biology*, eds. D. Marshak, D. Liu, pp. 23–30 (1989).

Physician's Desk Reference, Medical Economics Co., Oradell, NJ pp. 1193–1194 (1988).

Physician's Desk Reference, Medical Economics Co., Oradell, NJ pp. 1065–1050 (1992).

Physician's Desk Reference, Medical Economics Co., Oradell, NJ pp. 1266–1267 (1993).

The Merck Index, Merck & Co. Inc., Rahway, NJ p. 983, entry No. 7342 (1976).

The Merck Index, Merck & Co. Inc., Rahway, NJ p. 1203, entry No. 7537 (1989).

Merck Manual, Eleventh Ed., Merck & Co., 1989, pp. 1203–1207.

Primary Examiner—Paula K. Hutzell
Assistant Examiner—Bene: Prickril
Attorney, Agent, or Firm—Diane L. Marschang

[57] **ABSTRACT**

A stable pharmaceutically acceptable aqueous formulation containing human growth hormone, a buffer, a non-ionic surfactant, and, optionally, a neutral salt, mannitol, or, a preservative, is disclosed. Also disclosed are associated means and methods for preparing, storing, and using such formulations.

23 Claims, 5 Drawing Sheets

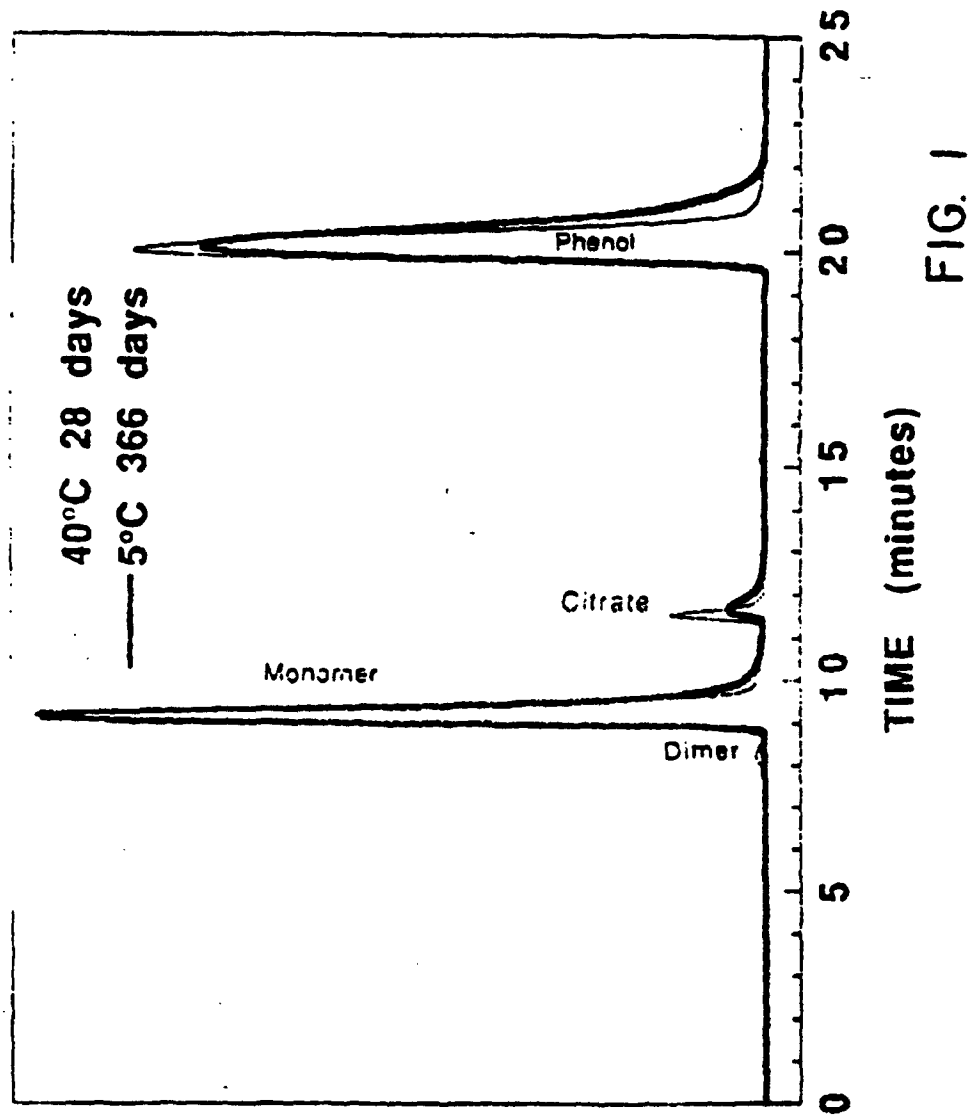
40°C 28 days
5°C 366 days
Phenol
Citrate
Monomer
Dimer
0
5
10
15
20
25
TIME (minutes)

FIG. 1

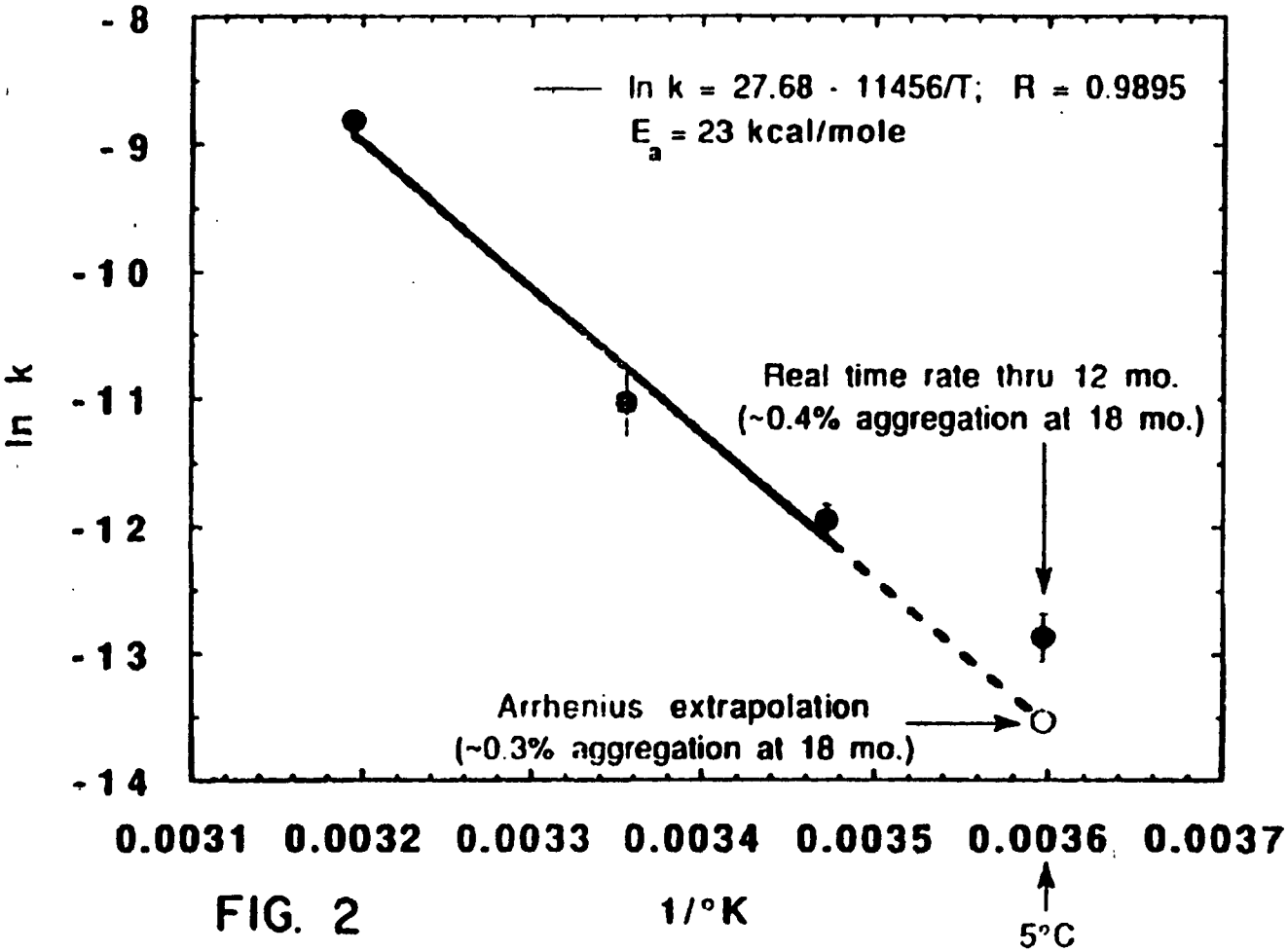
ln k = 27.68 - 11456/T; R = 0.9895
E_a = 23 kcal/mole
Real time rate thru 12 mo.
(~0.4% aggregation at 18 mo.)
Arrhenius extrapolation
(~0.3% aggregation at 18 mo.)
ln k
-8
-9
-10
-11
-12
-13
-14
0.0031 0.0032 0.0033 0.0034 0.0035 0.0036 0.0037
1/°K
5°C

FIG. 2

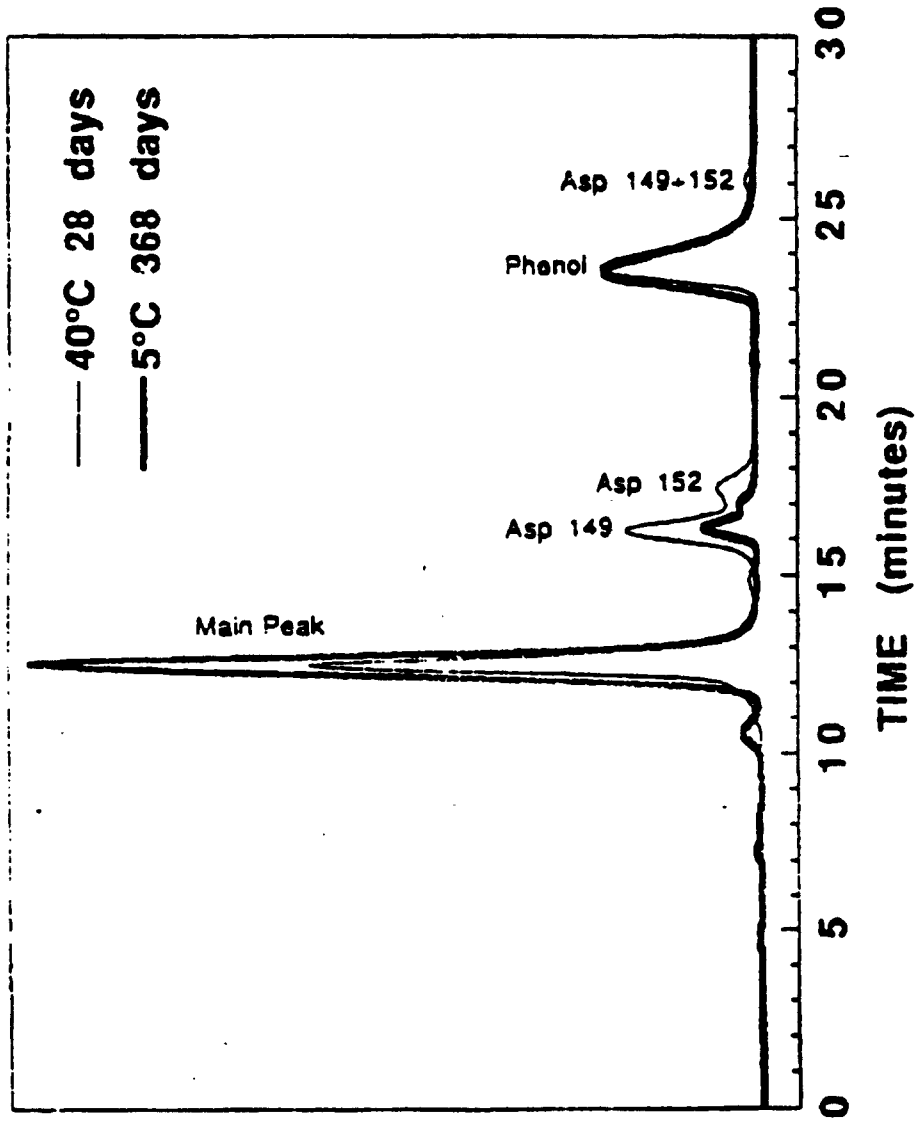
40°C 28 days
5°C 368 days
Asp 149+152
Phenol
Asp 152
Asp 149
Main Peak
0
5
10
15
20
25
30
TIME (minutes)

FIG. 3

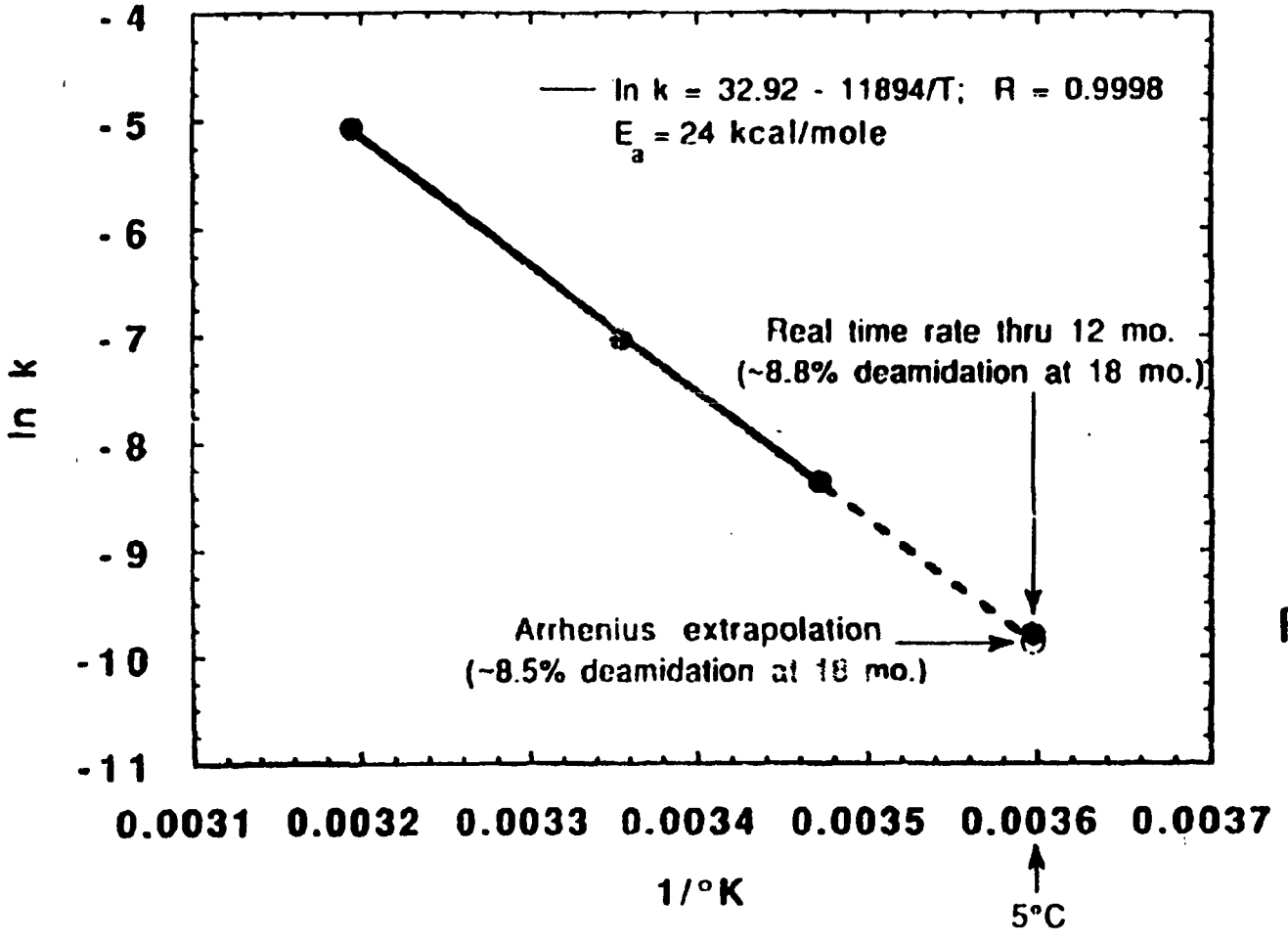
ln k = 32.92 - 11894/T; R = 0.9998
E_a = 24 kcal/mole
Real time rate thru 12 mo.
(~8.8% deamidation at 18 mo.)
Arrhenius extrapolation
(~8.5% deamidation at 18 mo.)
ln k
- 4
- 5
- 6
- 7
- 8
- 9
-10
-11
0.0031 0.0032 0.0033 0.0034 0.0035 0.0036 0.0037
1/°K
5°C

FIG. 4

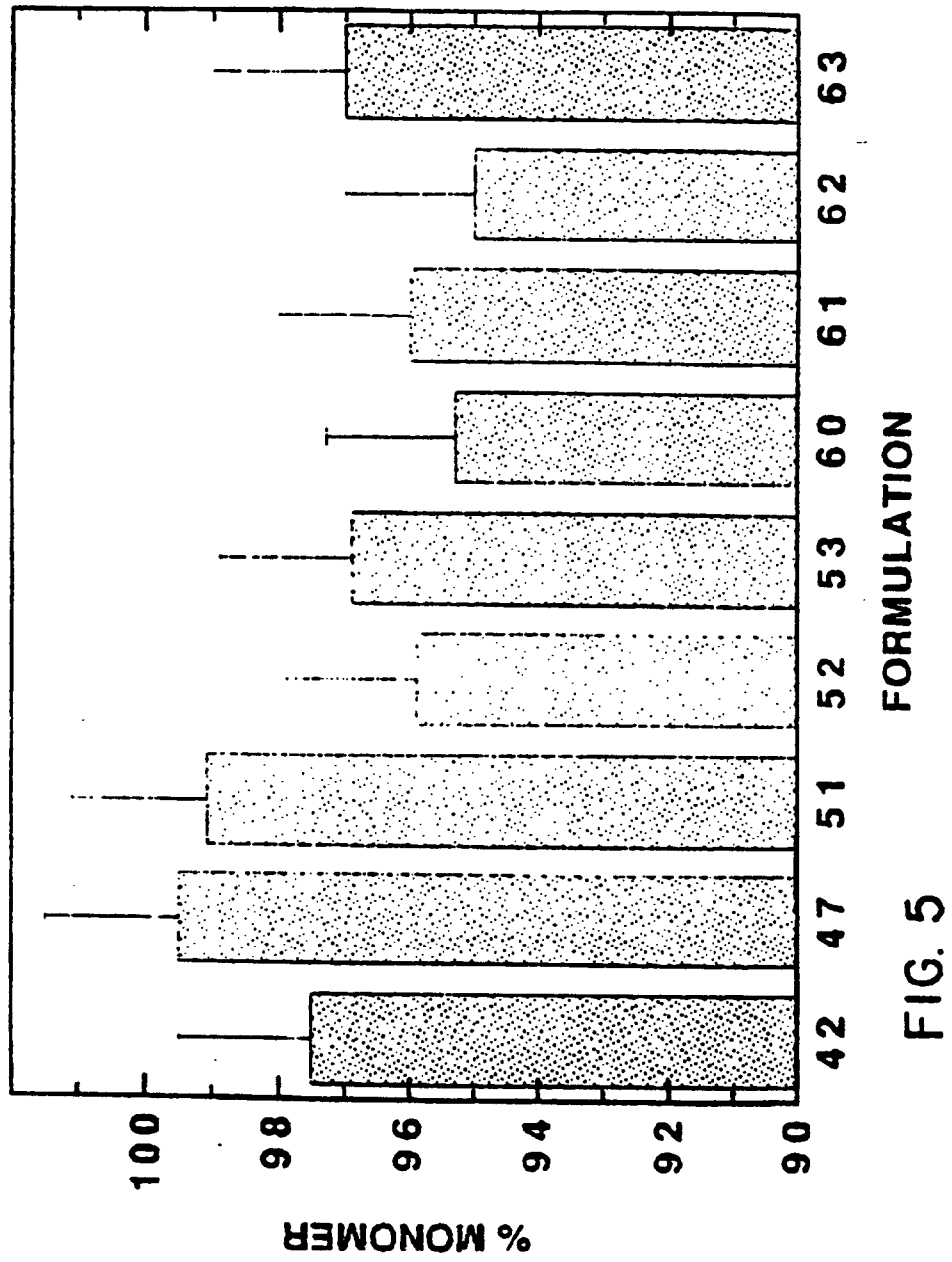

FIG. 5

HUMAN GROWTH HORMONE AQUEOUS FORMULATION

CROSS REFFRENCE TO RELATED APPLICATIONS

This case is a U.S. national stage application of PCT/US93/07149, filed Jul. 29, 1993, which is a continuation of U.S. patent application Ser. No. 07/923,401, filed Jul. 31, 1992, now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 07/751,424, filed Aug. 28, 1991, now abandoned, which is a continuing application of U.S. patent application Ser. No. 07/182,262, filed Apr. 15, 1988, now U.S. Pat. No. 5,096,885.

FIELD OF THE INVENTION

The present invention is directed to pharmaceutical formulations containing human growth hormone (hGH) and to methods for making and using such formulations. More particularly, this invention relates to such pharmaceutical formulations having increased stability in aqueous formulation.

BACKGROUND OF THE INVENTION

Human growth hormone formulations known in the art are all lyophilized preparations requiring reconstitution. Per vial, Protropin® hGH consists of 5 mg hGH, 40 mg mannitol, 0.1 mg monobasic sodium phosphate, 1.6 mg dibasic sodium phosphate, reconstituted to pH 7.8 (*Physician's Desk Reference*, Medical Economics Co., Oradell N.J., p. 1049, 1992). Per vial, Humatrope® hGH consists of 5 mg hGH, 25 mg mannitol, 5 mg glycine, 1.1 mg dibasic sodium phosphate, reconstituted to pH 7.5 (*Physician's Desk Reference*, p. 1266, 1992).

For a general review for growth hormone formulations, see Pearlman et al., *Current Communications in Molecular Biology*, eds. D. Marshak and D. Liu, pp. 23–30, Cold Spring Harbor Laboratory Press, Cold Spring Harbor N.Y., 1989. Other publications of interest regarding stabilization of proteins are as follows.

U.S. Pat. No. 4,297,344 discloses stabilization of coagulation factors II and VIII, antithrombin III, and plasminogen against heat by adding selected amino acids such as glycine, alanine, hydroxyproline, glutamine, and aminobutyric acid, and a carbohydrate such as a monosaccharide, an oligosaccharide, or a sugar alcohol.

U.S. Pat. No. 4,783,441 discloses a method for the prevention of denaturation of proteins such as insulin in aqueous solution at interfaces by the addition of up to 500 ppm surface-active substances comprising a chain of alternating, weakly hydrophilic and weakly hydrophobic zones at pH 6.8–8.0.

U.S. Pat. No. 4,812,557 discloses a method of stabilization of interleukin-2 using human serum albumin.

European Patent Application Publication No. 0 303 746 discloses stabilization of growth promoting hormones with polyols consisting of non-reducing sugars, sugar alcohols, sugar acids, pentaerythritol, lactose, water-soluble dextrans, and Ficoll, amino acids, polymers of amino acids having a charged side group at physiological pH, and choline salts.

European Patent Application Publication No. 0 211 601 discloses the stabilization of growth promoting hormones in a gel matrix formed by a block copolymer containing polyoxyethylene-polyoxypropylene units and having an average molecular weight of about 1,100 to about 40,000.

European Patent Application Publication No. 0 193 917 discloses a biologically active composition for slow release

characterized by a water solution of a complex between a protein and a carbohydrate.

Australian Patent Application No. AU-A-30771/89 discloses stabilization of growth hormone using glycine and mannitol.

U.S. Pat. No. 5,096,885 (which is not prior art) discloses a formulation of hGH for lyophilization containing glycine, mannitol, a non-ionic surfactant, and a buffer. The instant invention provides an unexpectedly stabilized aqueous formulation in the absence of glycine.

hGH undergoes several degradative pathways, especially deamidation, aggregation, clipping of the peptide backbone, and oxidation of methionine residues. Many of these reactions can be slowed significantly by removal of water from the protein. However, the development of an aqueous formulation for hGH has the advantages of eliminating reconstitution errors, thereby increasing dosing accuracy, as well as simplifying the use of the product clinically, thereby increasing patient compliance. Thus, it is an objective of this invention to provide an aqueous hGH formulation which provides acceptable control of degradation products, is stable to vigorous agitation (which induces aggregation), and is resistant to microbial contamination (which allows multiple use packaging).

SUMMARY OF THE INVENTION

One aspect of the invention is a stable, pharmaceutically acceptable, aqueous formulation of human growth hormone comprising human growth hormone, a buffer, a non-ionic surfactant, and optionally, a neutral salt, mannitol, and a preservative.

A further aspect of the invention is a method of preventing denaturation of human growth hormone aqueous formulations comprising mixing human growth hormone and a non-ionic surfactant in the range of 0.1–5% (w/v) (weight/volume). In yet another aspect of the invention, this stabilized formulation is stored for 6–18 months at 2°–8° C.

DESCRIPTION OF THE FIGURES

FIG. 1 is a size exclusion chromatogram of aqueous growth hormone formulation stored for 28 days at 40° C. (i.e., thermally stressed) and for one year at 5° C. (i.e., recommended conditions for storage).

FIG. 2 is a plot of Arrhenius rate analysis of growth hormone aggregation in aqueous formulation.

FIG. 3 is an anion exchange chromatogram comparing a thermally stressed (40° C.) aqueous formulation hGH sample with an aqueous formulation hGH sample stored under recommended conditions (2°–8° C.) for one year.

FIG. 4 is a plot of Arrhenius rate analysis of hGH deamidation in aqueous formulation.

FIG. 5 is a graph of the percentage monomer present in the various formulations where mannitol has been substituted with a neutral salt.

DETAILED DESCRIPTION OF THE INVENTION

A. Definitions

The following terms are intended to have the indicated meanings denoted below as used in the specification and claims.

The terms "human growth hormone" or "hGH" denote human growth hormone produced by methods including natural source extraction and purification, and by recombi-

nant cell culture systems. Its sequence and characteristics are set forth, for example, in *Hormone Drugs*, Gueriguian et al., U.S.P. Convention, Rockville, Md. (1982). The terms likewise cover biologically active human growth hormone equivalents, e.g., differing in one or more amino acid(s) in the overall sequence. Furthermore, the terms used in this application are intended to cover substitution, deletion and insertion amino acid variants of hGH, or posttranslational modifications. Two species of note are the 191 amino acid native species (somatropin) and the 192 amino acid N-terminal methionine (met) species (somatrem) commonly obtained recombinantly.

The term "pharmaceutically effective amount" of hGH refers to that amount that provides therapeutic effect in an administration regimen. The compositions hereof are prepared containing amounts of hGH at least about 0.1 mg/ml, upwards of about 10 mg/ml, preferably from about 1 mg/ml to about 20 mg/ml, more preferably from about 1 mg/ml to about 5 mg/ml. For use of these compositions in administration to human patients suffering from hypopituitary dwarfism, for example, these compositions contain from about 0.1 mg/ml to about 10 mg/ml, corresponding to the currently contemplated dosage regimen for the intended treatment. The concentration range is not critical to the invention, and may be varied by the clinician.

B. General Methods

The instant invention has no requirement for glycine. Glycine is an optional component of the aqueous formulation, although with less advantage in the aqueous formulations hereof compared with those formulations that are lyophilized for later reconstitution. Amounts of glycine will range from 0 mg/ml to about 7 mg/ml.

Non-ionic surfactants include a polysorbate, such as polysorbate 20 or 80, etc., and the poloxamers, such as poloxamer 184 or 188, Pluronic® polyols, and other ethylene/polypropylene block polymers, etc. Amounts effective to provide a stable, aqueous formulation will be used, usually in the range of from about 0.1% (w/v) to about 5% (w/v), more preferably, 0.1% (w/v) to about 1% (w/v). The use of non-ionic surfactants permits the formulation to be exposed to shear and surface stresses without causing denaturation of the protein. For example, such surfactant-containing formulations are employed in aerosol devices such as those used in pulmonary dosing and needleless jet injector guns.

Buffers include phosphate, Tris, citrate, succinate, acetate, or histidine buffers. Most advantageously, the buffer is in the range of about 2 mM to about 50 mM. The preferred buffer is a sodium citrate buffer.

A preservative is included in the formulation to retard microbial growth and thereby allow "multiple use" packaging of the hGH. Preservatives include phenol, benzyl alcohol, meta-cresol, methyl paraben, propyl parabens, benzalconium chloride, and benzethonium chloride. The preferred preservatives include 0.2–0.4% (w/v) phenol and 0.7–1% (w/v) benzyl alcohol.

Suitable pH ranges, adjusted with buffer, for aqueous hGH formulation are from about 4 to 8, more preferably about 5.5 to about 7, most advantageously 6.0 Preferably, a buffer concentration range is chosen to minimize deamidation, aggregation, and precipitation of hGH.

Mannitol may optionally be included in the aqueous hGH formulation The preferred amount of mannitol is about 5 mg/ml to about 50 mg/ml. As an alternative to mannitol, other sugars or sugar alcohols are used, such as lactose, trehalose, stachiose, sorbitol, xylitol, ribitol, myoinositol, galactitol, and the like.

Neutral salts such as sodium chloride or potassium chloride are optionally used in place of sugars or sugar alcohols. The salt concentration is adjusted to near isotonicity, depending on the other ingredients present in the formulation. For example, the concentration range of NaCl may be 50–200 mM, depending on the other ingredients present.

In a preferred embodiment, the formulation of the subject invention comprises the following components at pH 6.0.

Ingredient	Quantity (mg)
hGH	5
Sodium Chloride	6.8
Polysorbate 20	20
Sodium Citrate	2.5
Phenol	2.5
Sterile water	1 ml

It will be understood that the above quantities are somewhat flexible within ranges, as set forth in more detail above, and that the materials are interchangeable within the component categories. That is, polysorbate 80, or a poloxamer, may be substituted for polysorbate 20, a succinate or acetate buffer could instead be employed, and alternative preservatives and different pHs could be used. In addition, more than one buffering agent, preservative, sugar, neutral salt, or non-ionic surfactant may be used. Preferably, the formulation is isotonic and sterile.

In general, the formulations of the subject invention may contain other components in amounts not detracting from the preparation of stable forms and in amounts suitable for effective, safe pharmaceutical administration. For example, other pharmaceutically acceptable excipients well known to those skilled in the art may form a part of the subject compositions. These include, for example, various bulking agents, additional buffering agents, chelating agents, antioxidants, cosolvents and the like; specific examples of these could include trimethylamine salts ("Tris buffer"), and disodium edetate.

EXPERIMENTAL EXAMPLES

A. Assay Methods

Anion exchange chromatography (HPIEC) was run on a TSK DEAE 5PW column (1.0×7.5 cm) at 45° C. with a flow rate of 0.5 ml/min. The column was equilibrated in 50 mM potassium phosphate, pH 5.5, containing 10% (w/v) acetonitrile.

Elution was performed using a 25 minute gradient from 50–100 mM potassium phosphate, pH 5.5 with constant 10% (w/v) acetonitrile. The column load was 83 µg of protein. Detection was at 230 nM.

Nondenaturing size exclusion chromatography was run on a TSK 2000 SWXL column in 50 mM sodium phosphate, pH 7.2 containing 150 mM sodium chloride. The flow rate was 1 ml/min, with a 50–75 µg column load and detection at either 214 and 280 nm

Denaturing size exclusion chromatography was run on a Zorbax GF250 column in 200 mM sodium phosphate, pH 6.8–7.2/0.1% SDS. The flow rate was 1.0 ml/minute, with a with a 50–75 µg column load and detection at either 214 and 280 nm.

B. Formulation Preparation

In general, aqueous hGH formulation samples for analysis in these experimental examples were prepared by buffer exchange on a gel filtration column. The elution buffer contained either sodium chloride or mannitol, buffer and the non-ionic surfactant in their final ratios. This resulting

solution was diluted to a desired hGH concentration and the preservative was added. The solution was sterile filtered using a sterilized membrane filter (0.2 micron pore size or equivalent) and filled into sterile 3 cc type 1 glass vials, stoppered and sealed with aqueous-type butyl rubber stoppers and aluminum flip-off type caps.

The aqueous hGH formulation used in the experimental examples consisted of 5.0 mg somatropin (Genentech, Inc.), 45.0 mg mannitol, 2.5 mg phenol, 2.0 mg polysorbate 20, and 2.5 mg sodium citrate, pH 6.0, per ml of solution. The lyophilized formulation used as a reference for comparison in the examples consisted of 5.0 mg somatropin, 1.7 mg glycine, 45.0 mg mannitol, 1.7 mg sodium phosphate, 9 mg benzyl alcohol per ml sterile solution after reconstitution.

C. Example I

Chemical Stability of the Aqueous Formulation

Vials of the hGH aqueous formulation (lots 12738/55-102 and 12738/55-105) were incubated at either recommended storage temperatures of 2°–8° C., or elevated storage temperatures of 15° C., or 25° C., and then removed at various time points and assayed for changes in pH, color and appearance, and protein concentration. In addition, samples were incubated at 40° C. in order to study degradation patterns under extreme stress conditions. Degradation patterns for the aqueous formulation were also compared to the known degradation patterns for lyophilized growth hormone.

After storage at 2°–8° C. for up to one year, the aqueous formulation showed insignificant changes in pH, color and appearance, and protein concentration. Nondenaturing size exclusion HPLC performed on samples stored for up to one year at 2°–8° C. showed no significant aggregation of the drug product (FIG. 1). This result is unexpected in Light of the teaching of U.S. Pat. No. 5,096,885 that glycine contributes to preventing aggregation in the lyophilized preparation.

At temperatures above 8° C., little or no changes in pH or protein concentration were observed over time. Visual inspection revealed an increase in opalescence with time for samples stored at 40° C. This change was minimal during storage at 15°–25° C. and has not been observed during 2°–8° C. storage.

The amount of degradation product was calculated as an area percentage of the total hGH area of the chromatogram. The rate constant for each reaction was then calculated by subtracting the percentage of degradation product from 100%, taking the $\log_{10}$ and plotting against the time in days. The slope of a straight line to fit these data was used as the reaction constant (k). Arrhenius analysis was done by plotting the natural logarithm (ln) of the absolute value of each calculated reaction rate constant at 15°, 25°, and 40° C. as a function of the inverse absolute temperature and then extrapolating to 5° C. Arrhenius and real time rate analysis (FIG. 2) of data from the size exclusion HPLC indicate that the amount of growth hormone aggregation after 18 months of storage will be less than 1% (w/v).

Anion exchange HPLC analysis performed on the aqueous hGH formulation stored at 40° C. indicated an increase in acidic peaks over 28 days (FIG. 3). Three of these peaks, eluting at about 16, 17.5, and 26 minutes, were produced by hGH deamidation at positions 149, 152, and 149 plus 152. Arrhenius and real time rate analysis (FIG. 4) of data from this method, were plotted as described above, and indicate that the amount of deamidated hGH in these lots after 18 months of storage at 2°–8° C. will be about 9% (w/v). This

includes an initial amount of about 2.4% (w/v) deamidated hGH at time zero. Values as high as 15% (w/v) deamidation have been reported for other hGH products (Larhammar, H., et al., (1985) *Int. J. Pharmaceutics* 23:13–23). Although the rate of deamidation is faster in the aqueous state, this rate is minimized at pH 6.0 and below.

D. Example II

Physical Stability of the Aqueous Formulation

Each of six vials of lyophilized growth hormone were reconstituted with 1 ml bacteriostatic water for injection (BWFI) U.S.P. After dissolving, the contents were transferred to 3 cc vials, stoppered, and capped to provide the same configuration as that for the aqueous formulation. The six vials of the hGH aqueous formulation and six vials of reconstituted lyophilized hGH were vigorously shaken top to bottom in a horizontal fashion on a Glas-Col Shaker-in-the-Round at 240 jolts per minute using a stroke setting of 2.5, giving a horizontal displacement of 8±1 cm for up to 24 hours at room temperature to assess the effects of agitation on physical stability of the hGH aqueous formulation. All twelve samples were placed in a straight line on the shaker to assure that they were all exposed to the same force for each formulation. Two vials were removed for assays at 30 minutes, 6 hours, and 24 hours.

The results are displayed in Table I. Agitation produced very little change in the visual clarity of the aqueous formulation. There was no change in the content of total growth hormone monomer as detected by a nondenaturing size exclusion HPLC assay. This assay detects noncovalent aggregates, which are completely dispersed by SDS in a denaturing size exclusion HPLC assay.

By comparison, these results also demonstrated that the reconstituted lyophilized product was more sensitive to treatment, even after only 30 minutes of shaking. This sensitivity is typical for all currently available formulations of hGH, other than the aqueous formulation of the instant invention. The inclusion of the non-ionic surfactant is the most important factor in preventing this phenomenon from occurring.

TABLE I

Effects of Agitation at Room Temperature on hGH Aqueous Formulation vs. Reconstituted Lyophilized Formulation

Sample	Color/Appearance	% HPSEC Monomer	% Soluble Protein	% Total Monomer
Unshaken				
Aqueous	clear/colorless	98.7	ND	ND
Aqueous	clear/colorless	99.0	ND	ND
Lyophilized	clear/colorless	99.0	100	99.0
Lyophilized	clear/colorless	ND	ND	ND
Shaken 0.5 hr				
Aqueous	very slightly opalescent/colorless	99.0	100	99.0
Aqueous	very slightly opalescent/colorless	100.0	100	100.0
Lyophilized	slightly opalescent/colorless	99.6	100	99.6
Lyophilized	clear/colorless	92.8	100	92.8

TABLE 1-continued

Effects of Agitation at Room Temperature on hGH Aqueous Formulation vs. Reconstituted Lyophilized Formulation

Sample	Color/Appearance	% HPSEC Monomer	% Soluble Protein	% Total[1] Monomer
Shaken 6 hr				
Aqueous	slightly opalescent/ colorless	99.9	100	99.9
Aqueous	opalescent/colorless	99.4	100	99.4
Lyophilized	very opalescent/yellow to brown	89.5	79	98.8
Lyophilized	very opalescent/yellow to brown	72.7	61.7	44.9
Shaken 24 hr				
Aqueous	slightly opalescent/ colorless	99.8	ND	99.8
Aqueous	clear/colorless	99.8	ND	ND
Lyophilized	very cloudy/yellow to brown	60.6	21.5	13.0
Lyophilized	very cloudy/yellow to brown	56.7	14.8	8.4

[1]Total monomer = % monomer × % soluble protein/100

E. Example III

Preservative Effectiveness in the Aqueous Formulation

Samples of hGH aqueous formulation were subjected to bacterial challenge according to an abbreviated challenge using the standard U.S.P. test. In this test, a suspension of either *E. coli* or *S. aureus* was added to an aliquot of hGH aqueous formulation to give a final concentration of bacteria between 10^5 to 10^6 CFU/ml. Viable bacteria remaining in the tubes were counted immediately and after 4 and 24 hours incubation at 20°-25° C. The percentage change in the concentration of the microorganisms during the challenge was calculated according to the following equation:

$$\% \text{ initial titer} = \frac{\text{titer at } T = X \text{ hours} \times 100}{\text{titer at } T = 0}$$

The results of this experiment indicated that for two species of bacteria, concentrations of viable bacteria were reduced to less than 0.01% of the initial concentrations after 24 hours.

F. Example IV

Substitution of Mannitol with Salt

In this experiment aqueous formulations of hGH were compared that varied in concentrations of salt, mannitol, and non-ionic surfactant. All formulations contained 5 mg/ml hGH, 0.25% (w/v) phenol/10 mM sodium citrate, pH 6.0. Samples were stored 3–4 months at 2°–8° C. FIG. 5 indicates the percentage monomer present in the indicated formulations. The Table below indicates the composition of each formulation. These results demonstrate the unexpected stability of hGH in a formulation in which mannitol has been substituted with a neutral salt in the presence of a surfactant.

TABLE 3

Formulations Tested in FIG. 5

Formulation #	Composition
42	0.1% (w/v) polysorbate 20 50 mM mannitol
47	0.1% (w/v) poloxamer 188 0.1M NaCl
51	0.3% (w/v) polysorbate 20 50 mM mannitol
52	0.1% (w/v) poloxamer 188 50 mM mannitol
53	0.1% (w/v) poloxamer 184 50 mM mannitol
60	0.2% (w/v) polysorbate 20 0.1M NaCl
61	0.2% (w/v) polysorbate 20 0.05M NaCl
62	0.2% (w/v) polysorbate 20 0.15M NaCl
63	0.2% (w/v) polysorbate 20 50 mM mannitol

We claim:

1. A human growth hormone formulation comprising:
   a) 1 mg/ml to 20 mg/ml human growth hormone,
   b) buffer system providing pH 5.5 to pH 7,
   c) 0.1% w/v to 1% w/v nonionic surfactant, and
   d) 50 mM to 200 mM of neutral salt
   in a sterile injectable aqueous vehicle,
wherein said formulation is a long term cold temperature storage stable for 6 to 18 months at 2° to 8° C., directly injectable, pharmaceutically acceptable liquid, free of glycine and mannitol.

2. The formulation of claim 1 wherein the nonionic surfactant is a poloxamer.

3. The formulation of claim 2 wherein the poloxamer is poloxamer 188 or poloxamer 184.

4. The formulation of claim 1 wherein the nonionic surfactant is a polysorbate.

5. The formulation of claim 4 wherein the polysorbate is polysorbate 20 or polysorbate 80.

6. The formulation of claim 1 wherein the neutral salt is sodium chloride or potassium chloride.

7. The formulation of claim 1 wherein the buffer buffers the formulation to about pH 6.

8. The formulation of claim 1 wherein the buffer is selected from the group consisting of citrate, phosphate, Tris, succinate, acetate, and histidine buffers.

9. A human growth hormone formulation consisting essentially of:
   a) 1 mg/ml to 20 mg/ml human growth hormone,
   b) buffer system providing pH 5.5 to pH 7,
   c) 0.1% w/v to 1% w/v nonionic surfactant,
   d) 50 mM to 200 mM of neutral salt and
   e) a preservative,
   in a sterile injectable aqueous vehicle,
wherein said formulation is a long term cold temperature storage stable for 6 to 18 months at 2° to 8° C., directly injectable, pharmaceutically acceptable liquid free of glycine and mannitol.

10. The formulation of claim 9 wherein the nonionic surfactant is a poloxamer.

11. The formulation of claim 10 wherein the poloxamer is poloxamer 188 or poloxamer 184.

12. The formulation of claim 9 wherein the nonionic surfactant is a polysorbate.

13. The formulation of claim 12 wherein the polysorbate is polysorbate 20 or polysorbate 80.

14. The formulation of claim 9 wherein the neutral salt is sodium chloride or potassium chloride.

15. The formulation of claim 9 wherein the buffer buffers the formulation to about pH 6.

16. The formulation of claim 9 wherein the buffer is selected from the group consisting of citrate, phosphate, Tris, succinate, acetate, and histidine buffers.

17. The formulation of claim 9 wherein the preservative is selected from the group consisting of phenol, benzyl alcohol, meta-cresol, methyl paraben, propyl paraben, benzalkonium chloride, and benzethonium chloride.

18. A directly injectable aqueous human growth hormone formulation consisting of

5 mg/ml human growth hormone,

8.8 mg/ml sodium chloride,

2.0 mg/ml polysorbate 20,

2.5 mg/ml sodium citrate, and

0.5 mg/ml phenol

in a pH 6 buffered aqueous vehicle;

wherein said formulation is a long term cold temperature storage stable for 6 to 18 months at 2° to 8° C., directly injectable, pharmaceutically acceptable liquid, free of glycine and mannitol.

19. The formulation of claim 18 packaged in stoppered and capped sterile glass vials.

20. A method for using human growth hormone comprising the steps of

A) formulating said human growth hormone into an aqueous liquid formulation comprising:

a) 1 mg/ml to 20 mg/ml human growth hormone,

b) buffer system providing pH 5.5 to pH 7,

c) 0.1% w/v to 1% w/v non-ionic surfactant, and

d) 50 mM to 200 mM of neutral salt

in a pharmaceutically acceptable, injectable sterile aqueous vehicle, said formulation being free of glycine and mannitol;

B) storing said formulation as an aqueous liquid for from six to 18 months at 2° C. to 8° C. thereby forming a stored formulation; and

C) directly injecting said stored formulation into a patient in need of human growth hormone therapy.

21. A method for using human growth hormone comprising the steps of

A) formulating said human growth hormone into an aqueous liquid formulation consisting essentially of:

a) 1 mg/ml to 20 mg/ml human growth hormone,

b) buffer system providing pH 5.5 to pH 7,

c) 0.1% w/v to 1% w/v nonionic surfactant,

d) 50 mM to 200 mM of neutral salt and

e) a preservative,

in a pharmaceutically acceptable, injectable sterile aqueous vehicle said formulation being free of glycine and mannitol;

B) storing said formulation as an aqueous liquid for from six to 18 months at 2° C. to 8° C. thereby forming a stored formulation; and

C) directly injecting said stored formulation into a patient in need of human growth hormone therapy.

22. The method of claim 21 wherein in the aqueous liquid formulation:

the human growth hormone is present at 5 mg/ml,

the buffer system is a sodium citrate buffer providing pH 6,

the polysorbate nonionic surfactant is 2.0 mg/ml polysorbate 20,

the neutral salt is 8.8 mg/ml sodium chloride and

the preservative is 0.5 mg/ml phenol.

23. A method for using human growth hormone comprising the steps of

A) formulating said human growth hormone into an aqueous liquid formulation comprising:

a) 1 mg/ml to 20 mg/ml human growth hormone,

b) buffer system providing pH 5.5 to pH 7,

c) 0.1% w/v to 1% w/v non-ionic surfactant, and

d) 50 mM to 200 mM of neutral salt

in a pharmaceutically acceptable, injectable sterile aqueous vehicle;

B) storing said formulation as an aqueous liquid for from six to at least 18 months at 2° C. to 8° C. thereby forming a stored formulation, and

C) directly injecting said stored formulation into a patient in need of human growth hormone therapy

* * * * *

14. PATENT CERTIFICATION WITH RESPECT TO ANY PATENT WHICH CLAIMS THE DRUG

All investigations in this application were conducted by or for the applicant; hence, this section is not applicable.

Exclusivity Checklist

NDA: 20-522-013				
Trade Name: Nutropin AQ				
Generic Name: (somatropin [rDNA origin] injection)				
Applicant Name: Genentech, Inc.				
Division: DMEDP, HFD-510				
Project Manager: Crystal King				
Approval Date:				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes		No	✓
b. Is it an effectiveness supplement?	Yes	✓	No	
c. If yes, what type? (SE1, SE2, etc.)	SE-2			
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	✓	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.				
Explanation:				
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:				
Explanation:				
d. Did the applicant request exclusivity?	Yes		No	✓
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?				
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes		No	✓
If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE				

BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	✓
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (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) NOT APPLICABLE				
1. Single active ingredient product.	Yes		No	
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		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes		No	
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 <u>any one</u> 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).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. 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	✓	No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
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. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.				
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	✓	No	
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**				
Basis for conclusion:				
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	✓
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	✓
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:				
Investigation #1, Study #: M0380g	IND#			
Investigation #2, Study #:				
Investigation #3, Study #:				
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	✓
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
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	✓
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
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"):				
Investigation #1 M0380g	IND#			

Investigation #2					
Investigation #3					

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	Yes	✓	No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
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		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
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	✓
If yes, explain:				

BACK TO TOP

/S/

Signature of PM/CSO
Date: 3/22/00

Signature of Division Director
Da

/S/

cc:
Original NDA
Division File
HFD-93 Mary Ann Holovac

BACK TO TOP

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

/BLA # 20-522-013 Supplement # 013 Circle one(SE1) (SE2) SE3 SE4 SE5 SE6

Nutropin AQ (somatropin [rDNA origin])

HFD 510 Trade and generic names/dosage form: for injection Action: (AP) AE NA

Applicant Genentech Therapeutic Class growth hormone

Indication(s) previously approved (1) Pediatric patients: (1) long-term tx of growth failure due to lack of adequate endogenous GH secretion; (2) Tx of growth failure associated w/chronic renal insufficiency; (3) Tx of short stature & Turner's syndrome. (2) Adult patients: replacement of endogenous GH in those meet specified criteria.

Pediatric information in labeling of approved indication(s) is adequate ✓ inadequate ___

Proposed indication in this application no change in indication; (1) pubertal larger doses during adolescence

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? X **Yes (Continue with questions)** ___ **No (Sign and return the form)**

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

✓ Neonates (Birth-1month) ✓ Infants (1month-2yrs) ✓ Children (2-12yrs) ✓ Adolecents(12-16yrs)

✓ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.

- ___ (1) Studies are ongoing.
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ✓ **Yes** ___ **No**

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from clinical review (e.g., medical review, medical officer, team leader)

		3/24/00
Signature of Preparer and Title		Date

Orig NDA/BLA # 20-522-013
HFD-510/Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

16. DEBARMENT CERTIFICATION

[Section 306(k)(1) of the Act (21 U.S.C. 335a(k)(1)]

This is to certify that Genentech, Inc. has 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 Supplemental New Drug Application (NDA).

Signed by: _____

Robert L. Garnick, Ph.D

Title: Vice President, Regulatory Affairs

Date: 6/16/95

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 attachments	

✓ (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
Robert L. Garnick, Ph.D.	Vice President, Regulatory Affairs
FIRM/ORGANIZATION: Genentech, Inc.	
SIGNATURE: Robert L. Garnick	DATE: 6/10/99

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

Genentech, Inc.
Protocol M0380g

List of PI's and Sub-I's for FDA Financial Disclosure

Principal Investigator Name and Address	Sub-Investigator Names	Financial Disclosure
Gilbert P. **August**, MD Department of Endocrinology Children's Hospital National Med Center Washington, DC 20010		
Jennifer J. **Bell**, MD Columbia Presbyterian Medical Center Department of Pediatric Endocrinology, BHN-106 New York, NY 10032	None listed on 1572	
Dennis M. **Bier**, MD St. Louis Children's Hospital One Childrens Place St. Louis, MO 63110	None Listed on 1572	
Thomas **Foley** Jr., M.D. Children's Hospital of Pittsburgh Division of Endocrinology 3706 5th Ave. at DeSoto Street Pittsburgh, PA 15213-3417		
Ronald **Gotlin**, MD The Children's Hospital 1056 E. 19th Avenue Denver, CO 80218	None listed on 1572	
Madeline **Harbison**, MD New York Hospital – Cornell Med Center Dept of Pediatrics, Room N236 525 E. 68th Street New York, NY 10021		
Raymond **Hintz**, MD Dept of Pediatrics, 8-322 Stanford University Medical Center Stanford, Ca 94305		
Abby Solomon **Hollander**, MD Washington University Med. Center St Louis Children's Hospital Campus Box 8116, One Children's Place St. Louis MO 63110	None listed on 1572	
Nancy J. **Hopwood**, MD Professor of Pediatrics University of Michigan Medical Center D3249 MPB, Box 0718 Ann Arbor, MI 48109-0718	None listed on 1572	
Nelly **Mauras**, MD Nemours Children's Clinic PO Box 5720 Jacksonville, FL 32247		
Margaret **MacGillivray**, MD Children's Hospital of Buffalo 219 Bryant St. Buffalo, NY 14222		

Genentech, Inc.
Protocol M0380g

List of PI's and Sub-I's for FDA Financial Disclosure

Principal Investigator Name and Address	Sub-Investigator Names	Financial Disclosure
Wayne V. **Moore**, MD Children's Mercy Hospital Endocrine Department 2401 Gillham Road Kansas City, MO 64108	[redacted]	
Thomas **Moshang**, MD Dept of Endocrinology/Diabetes Children's Hospital of Philadelphia 34th and Civic Center Blvd. Philadelphia, PA 19104	[redacted]	
Katrina L. **Parker**, MD Russell D. **Cunningham**, MD Assistant Professor of Pediatric Endocrinology 1600 Seventh Avenue South, ACC 608 Birmingham, AL 35233	[redacted]	
Leslie P. **Plotnick**, MD Department of Pediatric Endocrinology Johns Hopkins Hospital, CMSC 3-110 600 North Wolfe Street Baltimore, MD 21287-3311	None listed on 1572	
Edward O. **Reiter**, MD Department of Pediatrics Baystate Medical Center 759 Chestnut Street Springfield, MA 01199	[redacted]	
Alan **Rogol**, MD, PhD University of Virginia Health Sciences Center Department of Pediatrics, MR4-3037 Charlottesville, Va 22908	[redacted]	
Karen **Rubin**, MD University of Connecticut Health Center Department of Pediatrics, Building 12 Farmington, CT 06030	None listed on 1572	
William E. **Russell**, MD Vanderbuilt University Medical Center Nashville, TN 37232-2579	[redacted]	
Paul **Saenger**, MD Montefiore Hospital, Division of Ped./Endo 111 E. 210 St. Bronx, NY 10467	None listed on 1572	
Dennis M. **Styne**, MD UC Davis MS-1A, Room 1134 Department of Pediatrics Davis, CA 95616	[redacted]	
Thomas **Wilson**, MD Department of Pediatrics SUNY Health Sciences Center, T-11 Stony Brook, NY 11794	[redacted]	

Genentech, Inc.
Protocol M0380g

List of PI's and Sub-I's for FDA Financial Disclosure

Principal Investigator Name and Address	Sub-Investigator Names	Financial Disclosure
David T. Wyatt, MD MACC Fund Research Center Dept. of Pediatrics 8701 Water Town Plank Road Milwaukee, WI 53226		

ATTACHMENT

Notes to Certification for Financial Interests of Clinical Investigators

Study M0380g

Questionnaire packages were sent via certified mail to all investigators and subinvestigators.

1) The following investigators/subinvestigators were unreachable because they are no longer at the study site:

[redacted]

Russell D. Cunningham (replaced by Katrina L. Parker)

[redacted]

[redacted]

2) No subjects were enrolled at Karen Rubin's site

3) No responses were received from the following subinvestigators at the time of submission, and following the sponsor's sending of a second letter via Federal Express.

[redacted]

OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

NDA 20-522-013 (SE2) Drug: Nutropin AQ

Applicant: Genentech, Inc. Chem/Ther/other Types: _____

CSO/PM: Crystal King Phone: 827-6423 MailCode: HFD-510

ACTION PERF. GOAL DATE: 4/28/00 DATE CKLIST CMPLTD: _____

Arrange package in the following order (include a completed copy of this **CHECKLIST**): Check or Comment

1. ACTION LETTER with supervisory signatures — AP ✓ AE ____ NA ____
   Are there any Phase 4 commitments? — Yes ✓ No ____
2. Have all disciplines completed their reviews? — Yes ✓ No ____
   If no, what review(s) is/are still pending? ____
3. LABELING (package insert and carton and container labels). — Draft ✓ / Revised Draft ____ / Final ____
   (If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.)
4. PATENT INFORMATION ✓
5. EXCLUSIVITY CHECKLIST ✓
6. PEDIATRIC PAGE ✓
7. DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992). ✓
8. Statement on status of **DSI's AUDIT OF PIVOTAL CLINICAL STUDIES** — NN
   If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status.
   If no audits were requested, include a memo expaining why.

9. REVIEWS & MEMORANDA:

DIVISION DIRECTOR'S MEMO	If more than 1 review for any	✓
GROUP LEADER'S MEMO	1 discipline, separate reviews	✓
MEDICAL REVIEW	with a sheet of colored paper.	✓
SAFETY UPDATE REVIEW	Any conflicts between reviews	✓
STATISTICAL REVIEW	must have resolution documented	✓
BIOPHARMACEUTICS REVIEW		✓
PHARMACOLOGY REVIEW (Include pertinent IND reviews)		NN - memo
Statistical Review of Carcinogenicity Study(ies)		-
CAC Report/Minutes		-
CHEMISTRY REVIEW		10/8/97
Labeling and Nomenclature Committee Review Memorandum		N/A
Date EER completed ____ (attach signed form or CIRTS printout) N/A		OK — No —
FUR needed ____ FUR requested ____		
Have the methods been validated? N/A		Yes (attach) — No —
Environmental Assessment Review / FONSI		Review NA FONSI —
MICROBIOLOGY REVIEW		NN
What is the status of the monograph?		-

10. **CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes** ✓
11. **MINUTES OF MEETINGS** ✓
    Date of End-of-Phase 2 Meeting N/A
    Date of pre-NDA Meeting N/A IND # —
12. **ADVISORY COMMITTEE MEETING MINUTES** N/A — Minutes — Info Alert —
    or, if not available, 48-Hour Info Alert or pertinent section of transcript. — Transcript — No mtg X
13. **FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS** NN
14. If approval letter, has **ADVERTISING MATERIAL** been reviewed? — Yes — No —
    If no and this is an AP with draft labeling letter, has advertising material already been requested? — Yes, documentation attached ____ / No, included in AP ltr ✓
15. **INTEGRATED SUMMARY OF EFFECTIVENESS** (from NDA) ✓

16. **INTEGRATED SUMMARY OF SAFETY** (from NDA) ✓

17. **FDA LETTERS & MEMOS** ✓

18. **APPLICANT'S LETTERS** ✓

19. **CHARGE AND HISTORY CARD** ✓

revision:1/16/98

Memo

To: NDA 19-676, Supplement #16

From: Robert S. Perlstein MD, Medical Officer

CC: Saul Malozowski MD, Team Leader

Crystal King, Project Manager

Date: 3/29/2000

Re: Amendment to Review of Study M0380g

The purpose of this amendment is to comment further on which baseline characteristics of pubertal children with growth hormone deficiency (GHD) impact the response to therapy in the high and standard dose groups. As stated in my primary review, based on subgroup analyses (requested from and supplied by the sponsor subsequent to the original NDA submission) **utilizing mean height standard deviation score (SDS) at near adult height as the primary outcome measure**, GHD patients whose baseline height SDS were close to normal (>-1) did not require a larger dose of recombinant human growth hormone (rhGH) during puberty to attain a satisfactory adult height. On the other hand, female gender and older age at baseline did **not** preclude a benefit from the larger dose of rhGH.

Subsequently, analyses performed by the Agency's statistical reviewer (not available prior to completion of my review) were brought to the attention of myself and my team leader by the statistical reviewer during labeling meetings. **Utilizing mean last measured height adjusted for baseline height as the primary outcome measure**, female subjects did not benefit significantly from the larger dose of rhGH, and in fact female subjects who were older at baseline grew less after treatment with the larger amount of rhGH (compared with the response observed in older females treated with the standard dose of rhGH). In contrast, male subjects of all ages appeared to benefit from the larger dose of rhGH. These results must be interpreted cautiously in view

of the small number of females participating in this study (7 in each dose group). Nonetheless, it was decided to present the results of this trial by gender in the label.

Robert Perlstein MD, FACP, FACE
Medical Officer

Saul Malozowski MD, PhD
Team Leader

CC: Original NDA 19-676; HFD-510 NDA 19-676
Original IND [redacted] HFD-510 IND [redacted]
HFD-510 RPerlstein, SMalozowski, CKing

ENVIRONMENTAL ASSESSMENT
NDA 20-522-013

The categorical exclusion from preparing an environmental assessment was granted (see Chemistry Review #2).

FILING MEETING MINUTES
7/27/99

Drug/Application: NDA 19-676/S-016 Genentech: Nutropin Pubertal Dosing
NDA 20-522/S-013 Genentech: Nutropin AQ

1. Filing Discussion:

- Clinical – No issues per Rob Perlstein and Saul Malozowski.
  - Note: Higher dose appears to be associated with acromegalic-type events. This may be an approval/labeling issue.
- Pharmacology – No issues per Dave Hertig.
- Micro—Not needed
- Devices—Not needed
- Project Management – Financial Disclosure included.
- Chemistry – No issues per Bill Berlin (via attached e-mail).
- Biopharmaceutics—Not needed per Rob Shore see review dated 7/21/99
- Biostatistics – No issues per Joy Mele (screening table attached).
  - Note: Need to review upcoming 4-month safety update to ensure there is sufficient patient data to satisfy safety criteria.
- DSI –No filling issues per Roy Blay.

2. Priority or Standard Review schedule: ~~Priority~~ Standard

3. Clinical Audit sites (list): Roy Blay will ascertain the number of patients per site from the sponsor and will then contact Rob Perlstein to determine review site.

4. Advisory Committee Meeting: ~~Yes~~ No

5. Review Timelines/Review Goal Date (with labeling):

   - MS Project timelines for the entire project and for individual disciplines were distributed. The UF_{10} for 19-676 s/016 is April 14, 2000, and April 28, 2000, for 20-522 s/013. Office level review is NOT required. ***Each discipline agreed that all reviews, with labeling, would be signed and delivered to Crystal King on or before Monday, February 28, 2000.***

NOTE: This supplement is available in the electronic document room.

ACCEPTED FOR FILING

5/1

Crystal King, Regulatory Project Manager

5/1

Saul Malozowski, Medical Team Leader

Attachments:
(1) e-mail from William Berlin dated 7/27/99
(2) 45-day screening by J. Mele

cc: NDA 19-676 s/016
NDA 20-522 s/013
HFD-510: C.King/S.Malozowski/R.Perlstein/D.Hertig/R.Steigerwalt/W.Berlin/S.Moore
R.Shore/H.Ahn/J.Mele/T.Sahlroot
HFD-344 R.Blay

To: NDA 20-522, Supplement #13

From: Robert S. Perlstein MD, Medical Officer

CC: Saul Malozowski MD, Team Leader

Crystal King, Project Manager

Date: 03/24/00

Re: Review of Safety Update

The Safety Update for NDA 20-522, Supplement #13 was submitted on 19 November 1999 by the sponsor, Genentech, Inc. The Safety Update reported safety data for Study M0380g between 2 June 1998 and 14 September 1999. An analysis of this safety data can be found in the Medical Officer's NDA review, specifically in the review of Study M0380g in the Safety Results section (pages 44-52).

151

Robert Perlstein MD, FACP, FACE
Medical Officer

151

Saul Malozowski MD, PhD
Team Leader

CC: Original NDA 20-522; HFD-510 NDA 20-522
Original IND ; HFD-510 IND
HFD-510 RPerlstein, SMalozowski, CKing

45-Day Screening of NDA's
Division of Biometrics II HFD-715

NDA #: 19-676 SE2 -016

Priority Classification: probably non-priority

Drug: Nutropin (somatropin for injection)

Sponsor: Genentech, Inc.

Number of Controlled Studies:

Indication: treatment of growth failure due to lack of endogenous growth hormone

Date of Submission: June 11, 1999

Date of 45-day Meeting: July 27, 1999

Statistical Reviewer: Joy Mele, M.S. (HFD-715)

Volume Numbers in Statistical Section: Volumes 1-8

Brief Summary of Controlled Clinical Trial

Study Number	# of Sites	Design	Treatment Arms (N)	Duration of Treatment
M0380	20 US	Open-label, randomized, ongoing of pubertal patients	0.3 mg/kg/wk (49) 0.7 mg/kg/wk (48)	Patients were followed until adult height (epiphyseal closure and no change in height for 12 months

FILE-ABILITY CONCERNS

ITEM (Section on pages 4-5 of the RTF Guidance document)	CHECK (NA if not applicable)
Index sufficient to locate necessary reports, tables, etc (1a)	Overall index not adequate – study report index good
Sufficient data listings and intermediate analysis tables to permit a statistical review (1c)	OK
Original protocols & subsequent amendments available in the NDA (1c)	YES
Endpoints and methods of analysis spelled out in the protocols and followed according to the study report (1c)	Protocol endpoint was adult height/ endpoint in study report is near-adult height. ANCOVA performed as described in the protocol
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made (1c)	Study is ongoing so this could be considered an interim analysis
Intent-to-treat analyses performed (1c)	Yes on primary variable
Effects of dropouts on primary analyses investigated (1c)	An ITT analysis in addition to evaluable patients analysis was done
Designs utilized appropriate for the indications requested (2a+c)	OK
Sufficient patient exposure to evaluate safety (3c, ICH E1A for chronic LT trt -1,500 total, 300-600 for 6 months, 100 for 1 year)	???? – only 48 exposed to highest dose
Safety and efficacy for gender, racial, and geriatric subgroups investigated (3d)	It seems that no subgroup analyses were performed probably due to the small number of patients
Data analyses to support proposed dosing performed (3f)	Yes
Data from primary studies submitted on diskette or as part of CANDA	Yes – new SAS datasets requested

HFD-510 DMEDP

Memo

To: The File

From: Crystal King, Regulatory Project Manager

Date: 04/12/00

Re: Pubertal Dosing Supplement Labeling

We have agreed upon and accepted the draft labeling as submitted by Genentech on April 10, 2000.

/S/

Sue-Jane Wang
Biometrics Reviewer

/S/

Robert Perlstein, M.D.
Medical Reviewer

cc: NDA 19-656/S-016
NDA 20-522/S-013
Division Files
HFD-510 R. Perlstein/S.Wang/C.King

WITHHOLD 1 PAGE (S)

MEMORANDUM

DATE: April 11, 2000

FROM: John K. Jenkins, M.D.
Acting Director, Division of Metabolic and Endocrine Drug Products
Director, Office of Drug Evaluation II

TO: NDA 19-676
NDA 20-522

SUBJECT: Overview of supplemental NDA review issues

Administrative

Supplement 016 was submitted by Genentech to the approved NDA 19-676 for Nutropin (somatoropin [rDNA origin] for injection) on June 11, 1999. This supplemental application was assigned a standard review. The 10-month user fee goal date for this application is April 14, 2000. A companion supplement (013) was submitted to NDA 20-522 for Nutropin AQ that cross references the Nutropin supplement and has an 10-month user fee goal date of April 28, 2000.

Clinical/Statistical

This supplemental NDA application proposes the addition of a higher dose of Nutropin (0.7 mg/kg/week versus the standard 0.3 mg/kg/week) for pubertal patients with growth hormone deficiency. In support of this new indication, the sponsor submitted the results of one open-label, randomized, multi-center trial in patients with growth hormone deficiency who were previously receiving the standard dose of GH and were in the early stages of puberty. Please refer to the medical review prepared by Dr. Perlstein and the statistical review prepared by Dr. Wang for details of this study and its results. Overall this study demonstrated that patients receiving the higher dose of GH had a significantly higher last measured height than those patients who continued to receive the standard dose of GH during puberty after a mean of 2.7 years of therapy. This increase in height was accomplished without a significant or worrisome increase in adverse effects of GH. An interesting observation was that patients who had a SD height score greater than –1.0 at baseline were able to attain normal adult heights with the standard dose regimen (mean SD height score at near-adult height = -0.1). This observation should be [redacted] to avoid over dosing such patients in clinical practice with GH. Overall the study results support a conclusion that the higher dose regimen is effective in achieving greater height in GH deficient patients during puberty than the standard regimen. Information is lacking regarding the dose response for GH in these patients; however, given the long-term nature of the studies to evaluate this endpoint and the safety of the higher dose regimen in the current study, requirements for additional dose-ranging studies do not appear warranted.

This supplemental application is approvable pending agreement on adequate labeling with the sponsor.

Pharmacology/Toxicology
The sponsor did not submit any new animal studies in support of this new indication and none are required.

Chemistry, Manufacturing, and Controls
The new dosage does not involve any changes in the drug product or manufacturing procedures.

Data Integrity
No audits of the pivotal clinical study were requested from the Division of Scientific Investigations due to the small numbers of patients enrolled at each study site and the well established efficacy of GH in treatment of GH deficient children.

Labeling
There are several remaining minor issues related to the presentation of the data from the high-dose study in the labeling that remain to be negotiated with the sponsor.

Recommendation
This supplemental application, and its companion supplement for Nutropin AQ (NDA 20-522/S013, should be APPROVED once adequate labeling text is agreed with the sponsor. The sponsor will be reminded in the approval letter of their phase 4 commitments to highlight adverse reactions that occur in patients receiving the high dose regimen in their annual report, their periodic reports, and any expedited reports.

cc:

HFD-510/Division File
HFD-510/Jenkins
HFD-510/King

From: Sue-Jane Wang, Ph.D.
Senior Mathematical Statistician
HFD-715

To: File

Date: April 10, 2000

Subject: NDA 20-522 SE2-013, Nutropin AQ

The review performed by me of NDA# 19-676 SE2-016 supports the sponsor's claim under this Nutropin AQ NDA supplement. No additional statistical review is needed. All pertinent information for NDA# 20-522 SE2-013 may be cross-referenced from the review performed for NDA# 19-676 SE2-016. A copy of the original review is attached for the file.

Concur

cc: Archival NDA# 19-676 SE2-016
Archival NDA# 20-522 SE2-013
HFD-510/SMalozowski, RPerlstein
HFD-510/CKing, CSO
HFD-715/Chron, ENevius, TSahlroot, SWang

WITHHOLD 2 PAGE (S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Genentech, Inc.	April 11, 2000
TELEPHONE NO. *(Include Area Code)* (650) 225-1202	**FACSIMILE (FAX) Number** *(Include Area Code)* (650) 225-1397
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 1 DNA Way South San Francisco, CA 94080-4990	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 20522, S-013

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
somatropin (rDNA origin) injection	Nutropin AQ®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
recombinant human growth hormone	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
liquid	10 mg vial	subcutaneous injection

(PROPOSED) INDICATION(S) FOR USE:
replacement of endogenous GH in patients with adult GH deficiency

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION labeling, and chemistry, manufacturing, and controls environmental assessment

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Genentech, Inc.
1 DNA Way
South San Francisco, CA
94080-4990

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
	1. Index
X	2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
[signature]	Robert L. Garnick, Ph.D. V.P., Regulatory Affairs	April 11, 2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
1 DNA Way, South San Francisco, CA 94080-4990	(650) 225-1202

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Genentech, Inc.	March 21, 2000
TELEPHONE NO. *(Include Area Code)* (650) 225-1202	FACSIMILE (FAX) Number *(Include Area Code)* (650) 225-1397
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 1 DNA Way South San Francisco, CA 94080-4990	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 20522, S-013

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
somatropin (rDNA origin) injection	Nutropin AQ®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
recombinant human growth hormone	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
liquid	10 mg vial	subcutaneous injection

(PROPOSED) INDICATION(S) FOR USE:
replacement of endogenous GH in patients with adult GH deficiency

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION response to request for information

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Genentech, Inc.
1 DNA Way
South San Francisco, CA
94080-4990

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
X	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Robert L. Garnick, Ph.D. V.P., Regulatory Affairs	March 21, 2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
1 DNA Way, South San Francisco, CA 94080-4990	(650) 225-1202

Please **DO NOT RETURN** this form to this address.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Genentech, Inc.	June 24, 1999
TELEPHONE NO. *(Include Area Code)* (650) 225-1202	**FACSIMILE (FAX) Number** *(Include Area Code)* (650) 225-1397

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*
1 DNA Way
South San Francisco, California, USA 94080-4990
License 1048

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE*

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 20-522

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
somatropin (rDNA origin) injection	Nutropin AQ®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
recombinant human growth hormone	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
liquid	10 mg vial	subcutaneous injection

(PROPOSED) INDICATION(S) FOR USE:
growth failure due to a lack of endogenous growth hormone

PLICATION INFORMATION

APPLICATION TYPE (check one) ■ NEW DRUG APPLICATION (21 CFR 314.50) □ ABBREVIATED APPLICATION (ANDA, AADA, 21CFR 314.94) □ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ■ 505 (b) (1) □ 505 (b) (2) □ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one) □ ORIGINAL APPLICATION □ AMENDMENT TO A PENDING APPLICATION □ RESUBMISSION □ PRESUBMISSION □ ANNUAL REPORT □ ESTABLISHMENT DESCRIPTION SUPPLEMENT □ SUPAC SUPPLEMENT □ EFFICACY SUPPLEMENT ■ LABELING SUPPLEMENT □ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT □ OTHER

REASON FOR SUBMISSION
To add additional pubertal dose to label

PROPOSED MARKETING STATUS (check one) ■ PRESCRIPTION PRODUCT (Rx) □ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 | THIS APPLICATION IS ■ PAPER □ PAPER AND ELECTRONIC □ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CALIFORNIA 94080-4990

ɔss References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs refer referenced in the current .plication)

NDA 19-676, IND 27,603

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry Section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2) ITEM 8.E: Phase I and II Final Reports
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Robert L. Garnick	Robert L. Garnick, Ph.D., Vice President, Regulatory Affairs	June 24, 1999

ADDRESS *(Street, City, State, and ZIP code)*	Telephone Number
1 DNA Way, South San Francisco, CA 94080-4990	(650) 225-1202