CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-075

CORRESPONDENCE

Memo

To: NDA 21-075 Review

From: Robert S. Perlstein MD, Medical Officer

CC: Saul Malozowski MD, Team Leader

Crystal King, Project Manager

Date: 11/22/99

Re: Review of Safety Update

The Safety Update for NDA 21-075 was submitted on 8 October 1999 by the sponsor, Genentech, Inc. The Safety Update reported safety data for Study [redacted]03-003 between June 1998 and June 1999. An analysis of this safety data can be found in the Medical Officer's NDA review, specifically in the review of Study [redacted]03-003 in the Safety Results section (pages 90-96).

/S/

Robert Perlstein MD, FACP, FACE
Medical Officer

/S/ 11/22/99

Saul Malozowski MD, PhD
Team Leader

CC: Original NDA 21-075; HFD-510 NDA 21-075
Original IND [redacted]; HFD-510 IND [redacted]
HFD-510 RPerlstein, SMalozowski, CKing

Printed by Crystal King

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 27-Oct-1999 10:33am
From: Saul Malozowski
MALOZOWSKIS
Dept: HFD-510 PKLN 14B32
Tel No: 301-827-6398 FAX 301-443-9282

TO: Crystal King (KINGC)

Subject: Re: DSI inspection: Depo GH

Crystal:
We have determined not to ask for an inspection for this NDA because the number of patients per center is quite small and it does not justify an inspection when the data so far are quite consistent form center to center.
>

Saul

APPEARS THIS WAY
ON ORIGINAL

Printed by Crystal King

Electronic Mail Message

ivity: COMPANY CONFIDENTIAL

Date: 22-Sep-1999 10:59am
From: Roy Blay
BLAYR
Dept: HFD-46 MPN1 107
Tel No: 301-827-7378 FAX 301-827-2075

TO: Crystal King (KINGC)

Subject: Re: FWD: NDA 21075 "Nutropin Depot" from Genentech. Inc. Letter date Sept 20, 1999

Per my conversatons with Dr. Malozowski and Perlstein in August, we are not currently scheduling any inspections for 2 reasons: (1) enrollment at each site is minimal (< 10 subjects per site), and (2) no clinical concerns have been raised to this point.

Inspections can be arranged if further review reveals them to be necessary. Please let me know as soon as possible if inspections should be needed.

Thanks,

Roy

APPEARS THIS WAY
ON ORIGINAL

December 21, 1999
Memorandum
To: The file NDA 21-075 Nutropin Depot (somatropin [rDNA origin] for injectable suspension) 12-22-99
From: Solomon Sobel M.D. Director Division of Metabolic and Endocrine Drug Products
Subject: Approval of the NDA

The indication is for the long-term treatment of growth failure due to a lack of endogenous GH (growth hormone) secretion.

The major issues in this evaluation were:
1. Is Nutropin Depot an acceptable alternative to daily injections of GH?

2. What populations may be treated with regard to either naive or previously treated status.

3. What is the optimal regimen of Nutropin Depot injections; is a once monthly or twice monthly regimen significantly different in efficacy results?

4. What is the safety profile of Nutropin Depot?

The major advantage of Nutropin Depot is that the dosing convenience may compensate for the somewhat lesser efficacy.
The pivotal studies were not concurrently controlled with daily injection regimens but it was clear that in the naive patients that historical controls indicated that there was about a 3 cm per year lesser response to Nutropin Depot than to the conventional daily regimens.
Patients who were chronically treated with daily injections of GH and then were switched to Nutropin Depot showed a decline in the growth rate from the immediately preceding treatment period of about 3.0 cm per year, also.(this latter deceleration was from a higher baseline value than seen in naive patients and exceeded historic projections of what one might expect in the gradual decrease in response to daily injections of GH).
Thus, if there are major issues of compliance with a regimen of daily injections, Nutropin Depot offers an alternative form of therapy, albeit, with a probable loss in growth rate improvement as compared to the results achieved with daily injections.

The optimal regimen was not clearly established. Three dose regimens were studied
0.75 mg once a month
0.75 mg twice a month
1.50 mg once a month.

The Sponsor had elected to stop studies on the 0.75mg once a month regimen for the reason of lack of efficacy although the results were not statistically inferior to the other regimens.

In any event, either a once a month dose of 1.5 mg or a 0.75 mg twice a month may be used. There seems to be an arithmetical advantage of the twice monthly regimen especially noted in naive patients but there is no statistical significance in the differences.The reviewing medical officer and I discussed the issue of the available regimens. We believe that both regimens should be approved to afford the physician alternatives for various degrees of compliance in patients. In any event response rates in individual patients will be readily observed and dosage regimens may be altered. We also recommend but do not mandate further studies to delineate the relative efficacies of the two approved Nutropin Depot regimens.

The major safety issue are very frequent local reactions to injection.
However, there is no systemic safety issue.
This safety concern is not a reason for non-approval.

Conclusion:
The Division recommends approval with the labeling stipulations we have communicated to the sponsor.

Solomon Sobel

cc: NDA 21-075
Division File
HFD 510: S. Sobel/C.King/S.Malozowski/R. Perlstein/R.Steigerwalt/D.Hertig/
S.Moore/H.Ahn/R.Shore/T.Sahlroot/J.Mele

DEPARTMENT OF HEALTH & HUMAN SERVICES Food and Drug Administration

Memorandum

Date: 11/9/99 /S/

From: Saul Malozowski
Medical Team Leader

Subject: Nutropin Depot, NDA 21-075. Team leader recommendations

To: Solomon Sobel /S/
Division Director, DMEDP

In assessing the information reviewed by all disciplines regarding this new growth hormone formulation for the treatment of growth hormone deficiency, it is apparent that this product is effective in inducing growth velocity acceleration when compared to baseline. The outcomes, however, were smaller than those reported in the medical literature and from similar studies reviewed at the FDA for numerous GH products, among those studies for the same GH product with different formulations. Although in this NDA no head to head comparison was made with any of these approved GH products, given the similarities in the inclusion criteria for the submitted protocols with those previously reviewed it is fair to state that this product is inferior to all currently approved GHs. This is particularly relevant for non-naïve patients that when switched to Nutropin Depot grew very poorly, when compared with previous daily GH treatment.

In the submitted documentation the sponsor claims that the outcomes of the studies show that this product performs as well as all other products available. This is true only for studies where GH dosing was not optimized and when GH was given three times a week. Currently daily or six times a week dosing have resulted in better growth velocity acceleration. Indeed, the strategy of dividing the weekly dose into more injections, six or seven per week, resulted in labeling changes early during this decade. The results in non-naïve patients also question whether it is desirable to switch these subjects from traditional therapeutic approaches to this new formulation.

There is agreement with the claims that the bone age advancement is less with this product. This outcome framed by the sponsor as an evidence that patients will achieve similar adult heights that those reported with other formulations fails to account for two issues: first, the passage of time that makes the patients older and therefore less responsive to intervention, and second a lower catch-up outcome that will be difficult to overcome in the future.

All these shortcoming will necessitate strong labeling comments to alert patients of what is known with other GH products as well statements addressing the need to switch to other products if no adequate growth acceleration is achieved in naïve patients and whether it is advisable to switch previously daily treated patients with GH to this Depot formulation.

Although the studies were small and the number of patients evaluated quite limited, they have dispelled our concerns regarding potential GH accumulation and the secondary development of acromegaloid signs and symptoms.

Another indirect indication of poorer efficacy was the great number of patients that when offered to continue on the new formulation declined. The number of injection site reactions that were exceptionally common may have also confounded these decisions. These reactions were pain during and after the injection as well as erythema, nodules, itchiness, lipoatrophy and edema. For each injection-received patients experienced approximately 2.5-3 additional symptoms of discomfort.

The emergence of additional rare adverse events that may occur with this new formulation were limited by the small patient population studied in the pivotal studies. This is not unique to Nutropin Depot and has also happened in most GH studies because GH deficiency is a very rare condition and studies to support new indications have been generally small.

Regarding the PK/PD of this product it is important to emphasize that two days after injection only approximately 20% of the total injected GH is still available. This may explain the modest outcomes seen in the studies. IGF-I, a relative adequate marker for GH action, returned to baseline days prior to the next dose, suggesting that patients receiving this product may not be properly treated in between doses. This is also hinted by the fact that two patients prone to develop hypoglycemia because GH deficiency did so during treatment, albeit at a lower than the to be marketed dose.

Conclusion:
I recommend approval of this product pending substantial modifications to the submitted label in order to properly reflect the findings of the studies and the issues discussed above.

Memo

To: NDA 21-075 Review

From: Robert S. Perlstein MD, Medical Officer

CC: Saul Malozowski MD, Team Leader

Crystal King, Project Manager

Date: 12/16/99

Re: Review of Financial Disclosure

A review of financial disclosure was not necessary because the sponsor certified that the clinical investigators had no financial arrangements with the sponsors of the covered studies.

/S/

Robert Perlstein MD, FACP, FACE
Medical Officer

/S/ 12/16/99

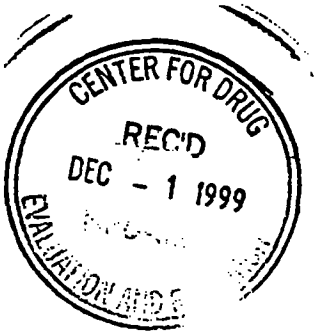
Saul Malozowski MD, PhD
Team Leader

CC: Original NDA 21-075; HFD-510 NDA 21-075
Original IND [redacted] HFD-510 IND [redacted]
HFD-510 RPerlstein, SMalozowski, CKing

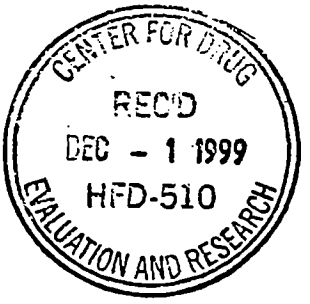
APPEARS THIS WAY
ON ORIGINAL

Genentech, Inc.

1 DNA Way
South San Francisco, CA 94080-4990
(650) 225-1000
FAX: (650) 225-6000



November 30, 1999



Solomon Sobel, M.D.,
Director
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 21-075** Nutropin Depot™
Amendment to a Pending Application
Item 4—Chemistry, Manufacturing and Controls
Item 6—Human Pharmacokinetics
Item 8—Clinical

Dear Dr. Sobel:

Genentech, Inc. is submitting the enclosed information to NDA 21-075 for Nutropin Depot [somatropin (rDNA origin) for injectable suspension]. For the record, we are submitting faxes that have been sent to the reviewers in response to their questions regarding Items 4, 6, and 8 of the application. In addition, we are also including responses to questions received on November 19, 1999 regarding the Chemistry, Manufacturing and Controls section of the NDA, and an update to the Stability section of the NDA. A complete desk copy of all the items is provided in a black binder for Ms. Crystal King, P.D., M.G.A., Project Manager. The review copies have been placed in the appropriate colored binders. Field copies of the Chemistry information have also been submitted to the San Francisco and Boston District offices.

Certification of Substantial Financial Support of Clinical Studies

Further to an inquiry by Ms. Crystal King, we hereby certify that Genentech, Inc. provided substantial financial support for the Nutropin Depot studies 03-001,

[redacted]03-002, [redacted]03-003, and [redacted]03-004. Genentech paid 100% of the cost of the studies, which were performed under contract by [redacted]

Stability Update

The stability update provides for the following dating periods for the various intermediates and drug product:

Intermediate/Product	Storage Conditions	Expiration Dating
rhGH Bulk Drug Substance in Bicarbonate Formulation	[redacted]	[redacted]
rhGH-Zinc Acetate Powder		
[redacted] rhGH Bulk Microspheres		
Nutropin Depot Final Product	2°C–8°C	24 months

An electronic archival copy of this submission on one CD has been submitted under separate cover to the CDER Central Document Room, according to the Guidance for Industry—Providing Regulatory Submissions in Electronic Format—General Considerations. Text is provided in Adobe Acrobat pdf format.

For help or information concerning any technical issues associated with the CD or electronic documents, please contact Mr. Scott Moore at (650) 225-7137 or Mr. Jan Van Gelder at (650) 225-1558. Please contact Mr. Art Blum, Director, at (650) 225-1559 if you have any questions regarding the Chemistry information. Please contact Ms. Fiona Cameron, Senior Manager, at (650) 225-1818, by fax at (650) 225-1397 or by email at cameron.fiona@gene.com if you have any other questions regarding the content of the application. We look forward to working with you during your review of this update.

Sincerely,

Roxanne Bates for RLG

Robert L. Garnick, Ph.D.
Vice President
Regulatory Affairs

21075-016 sub initials

HFD-510 DMEDP

Memo

APPEARS THIS WAY
ON ORIGINAL

To: The File

From: Crystal King, Regulatory Project Manager (S1)

Date: 12/14/99

Re: Nutropin Depot Labeling

We have agreed upon and accepted the draft patient package insert and immediate container and carton labels as submitted by Genentech on December 10, 1999, and the draft package insert labeling as submitted on December 14, 1999.

NAME	TITLE	SIGNATURE	DATE
Robert Perlstein, M.D.	Medical Officer	(S1)	12/15/99
Saul Malozowski, M.D., Ph.D.	Medical Team Leader	(S1)	12/14/99
Stephen Moore, Ph.D.	Chemistry Reviewer/Team Ldr.	(S1)	12/16/99
Dave Hertig	Pharmacology Reviewer	(S1)	12/15/99
Ron Steigerwalt, Ph.D.	Pharmacology Team Leader	(S1)	12/15/99
Joy Mele, M.S.	Biometrics Reviewer	(S1)	12/14/99
Todd Sahlroot, Ph.D.	Biometrics Team Leader	(S1)	12/14/99
Robert Shore, Pharm.D.	Biopharmaceutics Reviewer	(S1)	15-DEC-99
Hae-Young Ahn, Ph.D.	Biopharmaceutics Team Leader	(S1)	12/17/99

cc: NDA 21-075
Division Files
HFD-510: C.King

APPEARS THIS WAY
ON ORIGINAL

16 **Page(s) Redacted**

Draft

Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Div. Medical Imaging, Surg. & Dental Products (HFD-160) PKLN Room 18B-04, ATTN: Dr. Peter Cooney			FROM: Division of Metabolic and Endocrine Drug Products (HFD-510), PKLN Room 14B-04, Crystal King, P.D., Project Manager	
E: July 7, 1999	IND NO.:	NDA NO.: 21-075	TYPE OF DOCUMENT: New NDA	DATE OF DOCUMENT: June 25, 1999
NAME OF DRUG: Nutropin Depot	PRIORITY CONSIDERATION: PRIORITY		CLASSIFICATION OF DRUG: rHGH	DESIRED COMPLETION DATE: October 8, 1999

NAME OF FIRM: Genentech (contact: Art Blum, Director, Regulatory Affairs 650-225-1559 for CMC issues only)

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- X NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
  MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*: Micro Consult

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

To: Dr. Hussong 7/12/99

CENTER FOR DRUG REC'D JUL 8 1999 HFD-160 EVALUATION AND RESEARCH

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review and comment on new long-acting formulation. Total electronic archival submission is available on the network. DMEDP Chemistry Reviewer is Dr. William Berlin, ext. 7-6370. Thank You. Crystal King, Project Manager, ext. 7-6423.

cc: Original NDA 21-075
HFD-510/Div. Files
HFD-510/C.King/SMoore/WBerlin

SIGNATURE OF REQUESTER: Crystal King, P.D., M.G.A., Project Mgr. 07/07/99	METHOD OF DELIVERY (Check one): ☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

Printed by Crystal King

Electronic Mail Message

itivity: PRIVATE

Date: 13-Dec-1999 01:22pm
From: Robert Shore
SHORER
Dept: HFD-870 PKLN 14B04
Tel No: 301-827-6403 FAX 301-443-9282

TO: Crystal King (KINGC)

CC: Hae Young Ahn (AHNH)
CC: Robert Shore (SHORER)
CC: Stephen Moore (MOOREST)
Subject: Nutropin dissolution N21-075/N-000

C,

To date, the proposed [redacted] spec has gone through the following proposed transformations:
(NLT = not less than; NGT = not greater than)

Original proposed spec from Genentech:
[redacted]

FDA counter proposal:
[redacted]

Genentech counter proposal:
[redacted]

--

The FDA now proposes the following:
[redacted]

AND a phase 4 commitment to develop a [redacted] method that allows the generation of a meaningful [redacted] over [redacted] and a spec that includes [redacted] with a [redacted] spec at the first and second time point that is [redacted] at the last time point. A new proposed [redacted] should be submitted within one year.

Rob Shore

APPEARS THIS WAY
ON ORIGINAL

Printed by Crystal King

Electronic Mail Message

BEST POSSIBLE COPY

Sensitivity: PRIVATE

Date: 07-Dec-1999 11:09am
From: Robert Shore
SHORER
Dept: HFD-870 PKLN 14B04
Tel No: 301-827-6403 FAX 301-443-9282

TO: Fiona Cameron (cameron2@gene.com)

CC: Crystal King (KINGC)
CC: Robert Shore (SHORER)
Subject: Re: Clarification requested on Spec Change Proposal

Fiona,

-->Dear Dr. Shore:
-->
-->Thank you for the proposed spec change (to a [redacted] spec) for the
-->[redacted] I just wanted to confirm that your
proposal
-->is intended to replace the existing spec as it is written in the NDA.
-->Please let me know.
-->
-->We should be able to get back to you tomorrow (Tuesday) regarding the
-->acceptability of your proposal.
-->
-->Thanks again for your help
-->Regards
Fiona Cameron

-->

Yes, the recommendation for the [redacted] spec is to change/replace
your proposed [redacted] spec. The other [redacted] spec is acceptable
as is.

Robert M. Shore, Pharm.D.
Reviewer, Division of Pharmaceutical Evaluation-2
FDA

APPEARS THIS WAY
ON ORIGINAL

NDA 21-075
Division File

Printed by Crystal King
Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 06-Dec-1999 03:29pm
From: Crystal King
KINGC
Dept: HFD-510 PKLN 14B04
Tel No: 301-827-6423 FAX 301-443-9282

TO: Fiona Cameron (cameron2@gene.com@internet)

Subject: Biopharm Review

Fiona:
The attached recommendation is from Biopharm.
-Crystal

To: Fiona Cameron

APPEARS THIS WAY
ON ORIGINAL

- NDA 21-075
HFD 510 Division File

NDA 21-075 N-000 SUBMISSION DATE: 06/25/99

DRUG NAME: Nutropin Depot
REVIEWER: R. Shore, Pharm.D.
SPONSOR: Genentech

Our biopharmaceutics reviewer, Dr. Robert Shore, has completed his biopharmaceutics review of your June 25, 1999, submission. Following are his comments.

The [redacted] spec should be a [redacted] spec as follows to enhance discrimination: [redacted] Note: the [redacted] spec is acceptable.

Should you have any questions, please do not hesitate to contact me at 301-827-6423.

/S/ 12/6/99
Crystal Anne King, P.D., M.G.A.
Regulatory Project Manager

E-mail Clearance:

/S/ 12/6/99
Hae-Young Ahn, Ph.D.
Biopharmaceutics Team Leader

APPEARS THIS WAY
ON ORIGINAL

Printed by Crystal King

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 29-Nov-1999 08:46am
From: Crystal King 301-827-6423 FAX KINGC@A1
Dept:
Tel No:

TO: Fiona Cameron (cameron2@gene.com)
TO: kingc (kingc@A1)

Subject: Re: Telecon Monday - let me know your number

APPEARS THIS WAY
ON ORIGINAL

NDA 21-075
Division File

Patient Package Insert

Patient Package Insert was reviewed and found to be satisfactory with the exception of Section 8.

Section 8 as proposed by the sponsor:

Draft

Section 8 as revised by this reviewer:

Reactions at the injection site are frequent but usually do not last long. These include redness, bumps, pain during and after the injection, and itchiness.

If you notice any of the following signs or symptoms, contact your healthcare provider:

Occasionally a more severe reaction may develop at the injection site.

- Swelling or a lump that doesn't go away.
- Rash at the injection site.
- Any signs of infection or inflammation at an injection site (pus, persistent redness of surrounding skin that is hot to the touch, persistent pain after the injection).

Other severe reactions may include:

- Difficulty breathing.
- Body rash.

Printed by Crystal King

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 22-Nov-1999 07:10am
From: Crystal King 301-827-6423 FAX KINGC@A1
Dept:
Tel No:

TO: See Below
Subject: Re: Participants for Monday Call

Distribution:

TO: Fiona Cameron	(cameron2@gene.com)
TO: kingc	(kingc@A1)
CC: Saul Malozowski	(MALOZOWSKIS@A1)
CC: Robert Perlstein	(PERLSTEINR@A1)
CC: Joy Mele	(MELE@A1)
CC: Robert Shore	(SHORER@A1)

APPEARS THIS WAY
ON ORIGINAL

NDA 21-075
Division File

Fiona:
I have blocked out 1.5 hours for the call. I wanted to allow sufficient time for everyone to go off the phone, talk things out, and get back on, if necessary. My office is only a few doors away from the conference room, so I can run back and forth and do the e-mail thing. We can go some time later, if people are willing and not too frazzled.

My goal for today is first, to get understanding and commitment on the overall changes. Then, we will need to get as many specific changes agreed upon as possible. So, I propose that we have a brief time in the beginning for general discussion and questions. Then, we should start going page by page.

We do have time tomorrow morning--and I know you said Ken doesn't like early mornings!--to finish up. I would really like to have sign off by 4pm tomorrow on the labeling (we could stretch it to 11/29 if we have to, but everyone is off for the Thanksgiving days); otherwise we will have great difficulty in meeting our date. We have set an internal goal date of 12/10 due to scheduling of resources within the division. So, you can see we don't have much time. I hope we will be able to reach agreement quickly.

I will be in all morning, if you need to reach me..

~Crystal

Dear Crystal:

Thanks for the PI - I received it fine and in secure mode. Unfortunately we can't make a counterproposal until we hear the rationale for some of the changes, as some of them were a little unexpected. Ken did catch up with Saul, but we still want to have the call on Monday (1.30pm your time, I will call 301-443-3540) so that we can discuss the rationale further before making our counterproposal.

The participants from our side, in addition to me, are as follows:

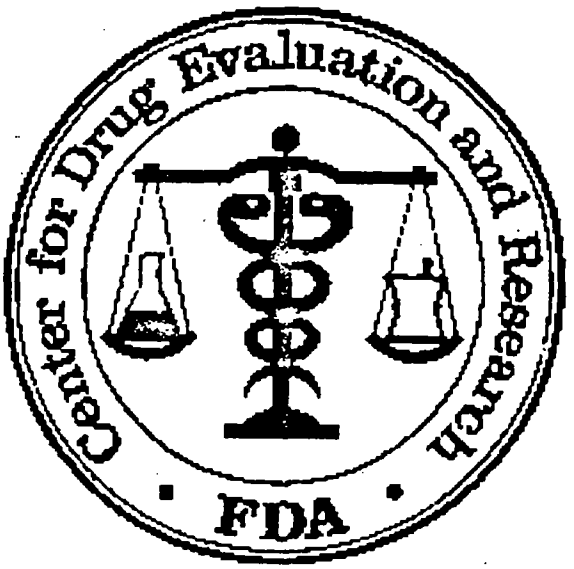
Ken Attie, M.D., Clinical
Paul Fielder, Ph.D., Pharmacokinetics and Metabolism David Perkins, GH Team Leader
Varun Nanda, ex-GH Team Leader, Marketing
Jeff Cleland, Ph.D, Depot Team Leader, Pharmaceutical R&D Rob Garnick, Ph.D., Vice President, Regulatory Affairs Roxanne Bales, Senior Director, Regulatory Affairs

How long did you plan on the call lasting? We have as much time as needed, but I wondered if there were any restrictions on your end.

Thanks, as usual, for your much-appreciated help, look forward to talking with you all on Monday
Fiona

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: November 19, 1999



Comments:

1. Additional Information Request for chemistry, manufacturing and controls information.
2. Updated list.

FAX Clearance:

/S/ 11/19/99
Stephen Moore, Ph.D.

TO:

Name Art Blum/Laura Vaughan

Fax No. 650-225-1397

Phone No. 650-225-4876

Location Genentech

FROM:

Name Crystal King, P.D., M.G.A.

Fax No. 301-443-9282

Phone No. 301-827-6423

Pages (including this cover sheet): 3

Additional Information Request for CMC information:

1. Please confirm that the Identity and Protein Content in-process control tests for rhGH Bulk Drug in Bicarbonate Formulation received at [redacted] from Genentech are the same as those described under Specifications and Analytical Methods for the Drug Substance.

2. The [redacted] test is performed as a part of the stability protocol for the final drug product. However, the [redacted] test is not performed. This latter method ensures that at least [redacted] of the rhGH can be released from Microspheres. The [redacted] test should be performed at least at end of expiry.

APPEARS THIS WAY
ON ORIGINAL

Subject: FWD: Re: 21-075 labeling
Date: Thu, 18 Nov 1999 08:51:37 -0500 (EST)
From: "Crystal King 301-827-6423 FAX 301-443-9282" <KINGC@cder.fda.gov>
To: "Fiona Cameron" <cameron2@gene.COM>

Encrypted and Signed

Fiona:
Attached is (1) e-mail transmission authorization from Saul and (2) our proposed labeling. Please note that there are several places with asterisks and italics--this is how I chose to set off "notes" to you--they are NOT to remain in the label. Also, I did not number the two tables. Finally, I know you are aware of the missing numbers in the efficacy section.

I will be away from the office tomorrow. Saul is available to answer any necessary questions from 2 to 3pm EST. We hope to have an e-mail response back from you Monday morning so we can discuss at our t-con at 1:30. Please call 301-443-3540.

Thanks,
Crystal

Subject: Re: 21-075 labeling
Date: Thu, 18 Nov 1999 08:36:30 -0500 (EST)
From: "Saul Malozowski 301-827-6398 FAX 301-443-9282" <MALOZOWSKIS@cder.fda.gov>
To: "Crystal King" <KINGC@cder.fda.gov>
CC: "Robert Perlstein" <PERLSTEINR@cder.fda.gov>, "Joy Mele" <MELE@cder.fda.gov>, "Robert Shore" <SHORER@cder.fda.gov>, "David Hertig" <HERTIG@cder.fda.gov>

"E-Mail transmission cleared"
Saul Malozowski

C:\MYDOCU~1\NDA\N21075\LABEL\PROP09~1.DOC	**Name:** C:\MYDOCU~1\NDA\N21075\LABE **Type:** Winword File (application/msword) **Encoding:**

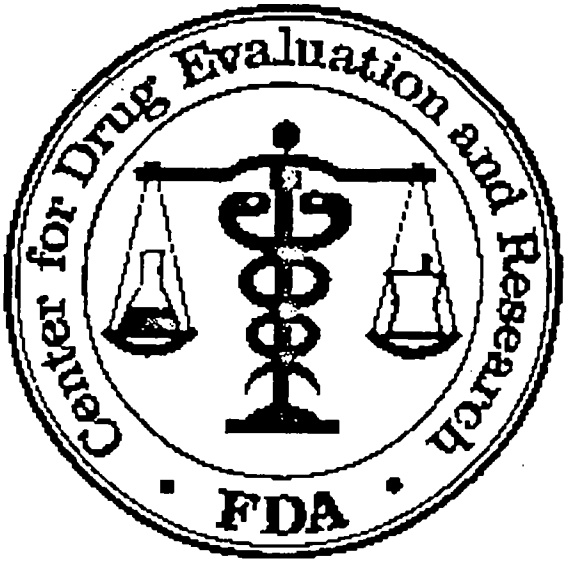
APPEARS THIS WAY
ON ORIGINAL

NDA 21-075
Div File

FOOD AND DRUG ADMINISTRATION

DATE: November 16, 1999

DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706



Comments:
Following is an information request for chemistry, manufacturing and controls information.

FAX Clearance:

/S/ 11/16/99
Stephen Moore, Ph.D.

TO:

Name Laura Vaughan

Fax No. 650-225-1397

Phone No. 650-225-4876

Location Genentech

FROM:

Name Crystal King, P.D., M.G.A.

Fax No. 301-443-9282

Phone No. 301-827-6423

Pages (including this cover sheet): Two (2)

Information Request for CMC information:

Drug Substance:

1. A reprocessing protocol (referred to as "recycling") is provided in the event the final bulk fails to meet specifications. Please verify that the reprocessing protocol will be utilized only once for a given batch and once for a given step. Also, please specify the frequency that the reprocessing protocol is anticipated to be utilized.

Drug Product:

2. Please confirm that the Identity and Protein Content in-process control tests for rhGH Bulk Drug in Bicarbonate Formulation received at [redacted] from Genentech are the same as those described under Specifications and Analytical Methods for the Drug Substance.

3. The Mean Particle Size specification for Bulk Microspheres should also include a limit for small particles.

4. Regulatory specifications for both the Bulk Microspheres and the final vialed products are considered necessary to ensure lot-to-lot consistency and shelf-life stability. However, the majority of the release and stability testing, including certain critical attributes, is actually performed separately on the Bulk Microspheres as in-process Certificate of Analysis (CoA) testing rather than on the final products. Therefore, a footnote should be added to the regulatory shelf-life specifications sheet for the final drug products that serves to incorporate the shelf-life specifications for the Bulk Microspheres that are not reiterated on the final product.

5. Poly D/L lactide-co-glycolide microspheres, following resuspension, may be expected to adhere to some extent to the vial and syringe component surfaces. The results of an in vitro study should be provided to demonstrate that the dose of rhHG actually delivered from the syringe needle is not significantly reduced by the potential adherence of micropheres.

6. A written justification should be provided to support the requested expiry of [redacted] months for the 13.5 mg/vial product although only [redacted] months real time stability data is available.

7. The [redacted] test is performed as a part of the stability protocol for the final drug product. However, the [redacted] test is not performed. This latter method ensures that at least [redacted] of the rhGH can be released from Microspheres. The [redacted] test should be performed at least at end of expiry.

Labeling:

8. In the Description section of the Physician's Package Insert, and all other places in the labeling, the phrase [redacted] is not applicable to this type of dosage form.

9. In the Description section of the Physician's Package Insert, the first sentence of the third paragraph [redacted] is redundant to the first sentence of the first paragraph, therefore should be deleted.

10. In the Description section of the Physician's Package Insert, the last sentence of the third paragraph [redacted] Should be revised to "Before administration, the powder is suspended in Diluent for Nutropin Depot, a sterile aqueous solution."

APPEARS THIS WAY
ON ORIGINAL

510 - King

HFD-510 DMEDP

File Memo

To: IND

From: Stephen Moore, Chemistry Team Leader /S/ 10/25/99

Date: 10/25/99

Re: NDA 21-075 Nutropin Depot

Chemist's response to unofficial FAX dated 10/20/99 from Genentech (see attached). The following questions were posed to the agency:

> "Is the proposal to revise the expiration dating for the rhGH-Zinc Acetate Powder to [redacted] months at [redacted] based on the 2L storage container moisture information acceptable?
>
> Is the proposal to place additional lots on stability to further support this dating acceptable?"

These proposals are **acceptable**. Submission of an amendment regarding this matter to the NDA is requested.

cc: NDA 21-075
Division File
HFD-510: SMoore/CKing

APPEARS THIS WAY
ON ORIGINAL

Genentech, Inc.

Fax Cover Sheet

Regulatory Affairs Department
1 DNA Way
South San Francisco, CA 94080
(650) 225-1000
TWX: 9103717168

To:	Dr. Stephen Moore CDER/ONDC
Fax Number:	301-443-9282
From:	Laura Vaughan
Fax Number:	650-225-1397
Date:	October 20, 1999
Re:	Nutropin Depot NDA 21-075
Number of Pages:	5

APPEARS THIS WAY
ON ORIGINAL

Dr. Moore,

Per our previous discussion, attached is information in preparation for a teleconference on Thursday, October 21, 1999 at 1:30 pm (EST). This teleconference is to discuss updated information on the proposed expiration dating for the process intermediate, rhGH-Zinc Acetate Powder relative to that contained in Genentech's Nutropin Depot NDA (21-075).

The proposed participants of this teleconference are:

Art Blum, Director, Regulatory Affairs, Genentech
JQ Oeswein, Ph.D, Associate Director, Quality Control Stability, Genentech
Glenn Hunt, Manager, Quality Control Stability, Genentech
Laura Vaughan, Associate, Regulatory Affairs, Genentech
Don Burstyn, Ph.D, Vice President, Regulatory Affairs, Alkermes
Pam Jaco, Senior Associate, Regulatory Affairs, Alkermes
Paul McGoff, Director, Quality Control, Alkermes
Carolyn Marcy, Stability Coordinator, Quality Control, Alkermes

We are looking forward to speaking with you. If you have questions, please do not hesitate to contact Laura Vaughan at (650) 225-4876.

Sincerely,

Laura Vaughan

Laura Vaughan
Associate, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Nutropin Depot NDA Stability Information for rhGH Zinc-Acetate Powder

BACKGROUND

The purpose of this submission is to update the Agency on current stability information related to the storage of the Nutropin Depot process intermediate, rhGH-Zinc Acetate Powder. This submission contains a proposal to revise the expiration date for the rhGH-Zinc Acetate Powder as shown in Table 1.

Table 1
rhGH-Zinc Acetate Powder Proposed Expiration Date

Nutropin Depot NDA Expiration Date[a]	Revised Expiration Date
[redacted]	[redacted]

[a] Section 4.A.3.g.1, Vol. 2, p. 222 contains initial (lot release) data from three rhGH-Zinc Acetate Powder consistency lots (10005, 10006 and 10008).

Recent stability results for these samples indicate that the model [redacted] storage containers utilized for the stability studies are not representative of manufacturing storage conditions, as assessed by residual moisture analysis. Stability studies on lots 10005, 10006, and 10008 have therefore been discontinued. Replacement lots will be added to the stability program once a model storage container, representative of that actually used for process intermediates, is identified.

RATIONALE FOR CHANGE

The 3-month timepoint for stability samples of lots 10005, 10006, and 10008 was recently completed. All results met specifications (i.e. protein integrity) with the exception of residual moisture. Moisture results for these stability samples are shown in Table 2. The moisture specification for rhGH-zinc acetate powder is [redacted] All 3-month results are significantly higher than those at initial lot release and all but one (lot 10008 at) are above specification.

To assess whether these results are representative of the intended commercial 2 L [redacted] storage container, a 2 L container of lot 10008 was removed from storage at ≤ – 20°C to a humidity-controlled isolator and sampled for residual moisture analysis. The results, shown in Table 3, indicate that moisture does not increase over time in this

container, and further indicate that the [redacted] containers used for stability studies are not representative of those actually used for process intermediates.

Table 2
rhGH-Zinc Acetate Powder Residual Moisture Content in Stability Lots
([redacted] Containers)

		Residual Moisture Content (%)	
Lot No.	Storage Temperature	Initial Lot Release	3 Months in Teflon Container
10005	2°C-8°C	-	22.4
	≤-20°C	5.1	10.4
10006	2°C-8°C	-	19.9
	≤-20°C	5.0	8.6
10008	2°C-8°C	-	21.9
	≤-20°C	4.6	7.7

Table 3
rhGH-Zinc Acetate Powder Lot 10008 Residual Moisture Content
(Manufacturing Storage in 2 L Teflon Container at ≤-20°C)

Timepoint	Residual Moisture Content (%)
Initial Lot Release	4.6
3 months	4.1
6 months	3.3

PROPOSAL

The current residual moisture data for rhGH-zinc acetate powder (lot 10008) support a recommended storage condition of 6 months at [redacted] in 2 L [redacted] containers. Once a representative model stability container is identified, three additional rhGH-Zinc Acetate Powder production lots (utilizing the to-be-marketed process) will replace lots 10005, 10006, and 10008 in the stability program. Data from these lots will be used to support or extend this proposed expiration dating.

A stability update to the Nutropin Depot NDA will be submitted in late November 1999 containing further information supporting the proposed expiration dating for rhGH-Zinc Acetate Powder, [redacted] rhGH Bulk Microspheres and Nutropin Depot Final Product.

QUESTIONS FOR THE AGENCY

Is the proposal to revise the expiration dating for the rhGH-Zinc Acetate Powder to 6 months at [redacted] based on the 2 L storage container moisture information acceptable?

Is the proposal to place additional lots on stability to further support this dating acceptable?

APPEARS THIS WAY
ON ORIGINAL

NDA 21-075 N-000 SUBMISSION DATE: 06/25/99

DRUG NAME: Nutropin Depot
REVIEWER: R. Shore, Pharm.D.
SPONSOR: Genentech

Our biopharmaceutics reviewer, Dr. Robert Shore, has completed his filing review of your June 25, 1999, submission. Following are his comments.

1. Although an annotated PI is included in the electronic document as a PDF file and the sponsor has also included a Word file of the proposed labeling, this reviewer would find it more useful if the sponsor could submit one PI in Word format with clear indications of what is currently approved for Nutropin NDA 19-676 (e.g., regular text) and what are proposed changes (e.g., highlighted or colored text). This would expedite the review writing process.

2. The sponsor should provide intra/inter-assay precision and accuracy data from the actual assay runs conducted on IGF-1. This submission includes only the kit insert but this does not allow an evaluation of the assay's performance during actual analysis of samples from the clinical studies. Also, the sponsor should submit accuracy data for the GHBP assay. If this information is available in the submission, please indicate where it can be found.

Should you have any questions, please do not hesitate to contact me at 301-827-6423.

/S/ 10/1/99
Crystal Anne King, P.D., M.G.A.
Regulatory Project Manager

APPEARS THIS WAY
ON ORIGINAL

Fax Clearance:

/S/
Hae-Young Ahn, Ph.D.
Biopharmaceutics Team Leader

APPEARS THIS WAY
ON ORIGINAL

MESSAGE CONFIRMATION

10/08/99 09:54
ID=FDA CDER DMEDP

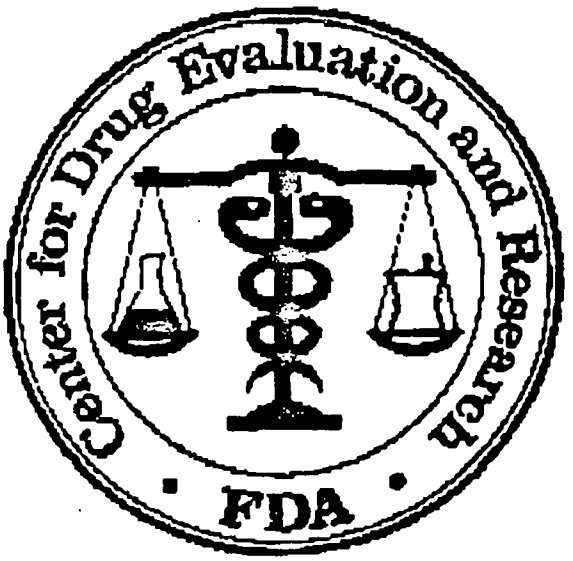
DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
10/08	00'49"	916502251397	CALLING	02	OK	0000

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: October 8, 1999

Comments:
Following are preliminary diluent label comments, per your request.

-Crystal



1 **Page(s) Redacted**

Draft

Labeling

Printed by Crystal King

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 01-Oct-1999 08:46am
From: Crystal King
KINGC
Dept: HFD-510 PKLN 14B04
Tel No: 301-827-6423 FAX 301-443-9282

TO: Fiona Cameron (cameron2@gene.com@internet)

CC: Crystal King (kingc)
CC: Robert Perlstein (PERLSTEINR)
Subject: 21-075

Fiona:
Please expect Dr. Perlstein to call with some requests for some additional information on injection site reactions.
Thanks,
Crystal

APPEARS THIS WAY
ON ORIGINAL

NDA 21-075
Division File

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: September 8, 1999
FDA participants: Saul Malozowski, M.D., Ph.D., Medical Team Leader (Acting) Crystal King, P.D., M.G.A., Regulatory Project Manager Robert Perlstein, M.D., Medical Reviewer Joy Mele, M.S., Biometrics Reviewer Purpose: To discuss the proposal for the efficacy update. R. Perlstein had forwarded questions earlier. 1. Why was the 0.75 mg monthly dose dropped? K. Attie explained that there was inadequate efficacy and safety demonstrated. 2. Explain the two proposed exclusion categories (0.75 dose and all CTs). Five normals were started at the low dose; it clouds the data after increasing the dose. **J. Mele requested data on the 18 patients included in the data set.** 3. Consideration of separate anlaysis for annual growth rate for CTs. Not applicable. 4. Should the 3 x 0.75 dose patients be excluded from the total of 13? Were the 002 study patients appropriately excluded? There were 13 patients each; the 0.75 doses have been broken out for each one. 5. Is the annualized growth rate that is known for each of the three groups (N002, N004, CT002) equally distributed? Why are CT rates missing for some patients? There is a subset analysis for some of the pre-treatment. Most had patient height; but it is limited for an annualized growth rate. **The second table in the update has analysis for a subset of 55; 14 don't.** 6. What happened to the 13/69 N004 patients?	**NDA#: 21-075** **Telecon/Meeting initiated by:** ○ Applicant/Sponsor ● FDA **By:** Telephone **Product Name:** Nutropin Depot **Firm Name:** Genentech **Name and Title of Person with whom conversation was held:** Ken Attie, M.D., Senior Clinical Scientist Ann Boche, Senior Mgr., Statistical Programming Tim Breen, Ph.D., Assoc. Director, Biostatistics Jeff Cleland, Ph.D., Sr. Scientist, Pharmaceutical Research & Development Fiona Cameron, Sr. Mgr., Regulatory Affairs Teresa Pechulis Buono, Director, Regulatory Affairs, Alkermes, Inc. John Loewy, Ph.D., Director, Biostatistics,

The patients will be indicated as D/C's; they will be in the safety update.

7. Issue of ITT analysis for all 35 of the 002 patients moved into the 003 study.
13 were D/C'd; 7 were not happy with the growth achieved. The numbers may have pooled 003 and 004.

In the original data sets, a secondary endpoint was added: Bayley-Pinneau predicted adult height.

/S/ 9/24/98

Saul Malozowski

/S/

Crystal King

Phone: 650-225-1818

cc: NDA 21-075
Div Files
HFD-510: S.Malozowski/C.King/R.Perlstein/J.Mele

Genentech, Inc.
Genentech, Inc.
Genentech, Inc.
Genentech, Inc.
Genentech, Inc.

1 DNA Way
South San Francisco, CA 94080-4990
(650) 225-1000

To: Crystal King, P.D., M.G.A.	To:
Fax: 301 443 9282	Fax:
Company: FDA	Company:
Dept: DMEDP	Dept:

From: Fiona Cameron, Regulatory Affairs
Tel: (650) 225-1818
Fax: (650) 225-1397

Date: 11/22/99

Number of Pages: 3 (including this one)

Reference: Nutropin Depot™ NDA 21-075

Dear Crystal:

Attached as you requested is a copy of the orphan drug designation letter.

Best regards

Fiona Cameron
cameron2@gene.com

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

October 28, 1999

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

Attention: Robert L. Garnick, PhD
VP, Regulatory Affairs

Dear Dr. Garnick:

Reference is made to your orphan designation application of June 1, 1998, submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act for the designation of somatropin (rDNA origin) as an orphan drug (application #[redacted]). We also refer to your amendment dated March 23, 1999.

We have completed the review of this application and the amendment and have determined that somatropin (rDNA origin) qualifies for orphan designation for the long-term treatment of children who have growth failure due to a lack of adequate endogenous growth hormone secretion. Long term administration is defined as one injection per month. Please note that this designation applies only to the long acting formulation.

Please be advised that if somatropin (rDNA origin) were approved for an indication broader than the orphan designation, your drug 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 drugs 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.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of somatropin (rDNA origin) as designated. Also an annual progress report must be submitted within 14 months after the designation date and annually thereafter until a marketing

application is approved [21 CFR 316.30]. If you need further assistance in the development of your drug for marketing, please feel free to contact John J. McCormick, MD, at (301) 827-3666.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

Sincerely yours,

/S/

Marlene E. Haffner, MD, MPH
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

APPEARS THIS WAY
ON ORIGINAL

JUL 22 1999

NDA 21-075

Genentech, Inc.
Attention: Robert L. Garnick, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Garnick:

Please refer to your pending new drug application (NDA) submitted dated June 25, 1999, received June 28, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nutropin Depot (somatropin [rDNA origin] for injection) .

We also refer to our letter dated July 8, 1999, acknowledging receipt of this NDA. At that time, we informed you that we would determine the therapeutic classification prior to the filing date. We have now ascertained that this application is a **Priority (P)** application and that it is fileable. Accordingly, the user fee goal date will be December 28, 1999.

If you have any questions, contact Crystal King, P.D., M.G.A., Regulatory Project Manager, at (301) 827-6423.

Sincerely,

/S/ 7.21.99

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

510 / /S/

NDA 21-075

JUL - 8 1999

Genentech, Inc.
Attention: Robert L. Garnick, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Garnick:

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:	Nutropin Depot (somatropin [rDNA origin] for injectable suspension)
Therapeutic Classification:	to be determined prior to the filing date
Date of Application:	June 25, 1999
Date of Receipt:	June 28, 1999
Our Reference Number:	21-075

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 August 27, 1999, in accordance with 21 CFR 314.101(a).

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:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact Crystal King, P.D., M.G.A., Regulatory Project Manager, at (301) 827-6423.

Sincerely,

/S/ 7.6.99

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

FILING MEETING
7/19/99

Drug/Application: NDA 21-075 Genentech: Nutropin Depot

1. Filing Discussion:

- Clinical – No issues per Saul Malozowski. (Rob Perlstein was absent.)
- Pharmacology – No issues per Dave Hertig and Ron Steigerwalt.
- Micro – Dave Hussong not present; however, attached e-mail states "no filing issues."
- Devices – Not applicable.
- Project Management – Financial Disclosure included.
- Chemistry – No filing issues per William Berlin and Stephen Moore.
  - A stability update is scheduled until December, 1999; this will not affect filing, but may be addressed through the expiration dating granted, if necessary.
  - Stephen Moore expressed concern over the consistency of dose delivery due to bead adherence to the syringe device and due to a large [redacted] overage in the vials.
  - ***Crystal King will check with the sponsor to ensure that inspection sites will be ready.***
- Biopharmaceutics – No issues per Rob Shore and Hae-Young Ahn.
- Biostatistics – Nothing to prevent filing per Joy Mele and Todd Sahlroot.
  - Joy presented a screening table for fileability issues (attached).
  - ***Crystal King will check that at least 100 patients will have completed one year in the study by the time of the scheduled October safety update.***
- DSI – Roy Blay noted that this is a multi-center application. However, the largest site covered only seven patients. DSI policy is not to inspect for fewer than ten patients, unless the review Division has a particular concern. No filing issues.

2. Priority or Standard Review schedule: Priority [redacted]

3. Clinical Audit sites (list): (see above) ***Saul Malozowski will notify Roy Blay ASAP should any sites need to be evaluated.***

4. Advisory Committee Meeting: No

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

   - MS Project timelines for the entire project and for individual disciplines were distributed. The UF_6 for this Priority submission is December 28, 1999. 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, November 8, 1999.***

   - Joy Mele and Bill Berlin have accessed the electronic archival submission without difficulty.

   - Due to the recent implementation of pre-Rounds, a full team meeting will not be scheduled for at least two months, unless necessary.

ACCEPTED FOR FILING

/S/

Crystal King, Regulatory Project Manager

/S/ 11/9/99

Saul Malozowski, Medical Team Leader

APPEARS THIS WAY
ON ORIGINAL

Attachments:
(1) e-mail from David Hussong dated 7/13/99
(2) 45-day screening by J. Mele dated 7/19/99

cc: Original NDA 21-075
HFD510: C.King/S.Malozowski/R.Perlstein/D.Hertig/R.Steigerwalt/W.Berlin/
S.Moore/R.Shore/H.Ahn/J.Mele/T.Sahlroot
HFD-160: D.Hussong/P.Cooney
HFD-344: R.Blay

Printed by Crystal King

Electronic Mail Message

..sitivity: COMPANY CONFIDENTIAL

Date: 13-Jul-1999 04:12pm
From: David Hussong
HUSSONG
Dept: HFD-160 PKLN 18B08
Tel No: 301-827-7340 FAX 301-480-6036

TO: Peter Cooney (COONEY)

CC: Crystal King (KINGC)
Subject: [redacted] Depot NDA 21-075

Peter,

Crystal King (HFD-510) called yesterday about this NDA's filing meeting, which is July 19. We attended the pre-NDA meetings. I found the jackets next to your desk, and looked at them briefly to answer the filing question.

Like most submissions that follow the 1993 Guideline, this one lacks background information that generally describes the product, but that can be filled in since the complete NDA is on the network drive (if the network is operating). There is a DMF for the diluent component, a micro section to the NDA and an electronic submission.

The submission is "filable." Review time will be a while (even though this is a "priority NDA") since each of us is backed up.

eturned the jackets to your desk.

avid

N.B.: Crystal - Please let us know the "path" to the electronic NDA file.

APPEARS THIS WAY
ON ORIGINAL

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

NDA #: 21-075

Priority Classification: possibly priority

Drug: Nutropin Depot (somatropin)

Sponsor: Genentech, Inc.

Number of Controlled Studies: 0, 2 uncontrolled studies

Indication: Treatment of growth failure due to lack of adequate endogenous growth hormone secretion

Date of Submission: June 25, 1999

Date of 45-day Meeting: July 19, 1999

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

Volume Numbers in Statistical Section: Volumes 1-6

Brief Summary of Clinical Trials

Study Number	# of Sites	Design	Treatment Arms (N)	Duration of Treatment	Comments
[redacted]03-002	12	Open label, randomized	0.75 1xmonth (19) 0.75 2xmonth (20) 1.5 1xmonth (25) Total N=64	6 months	Naïve and currently treated patients
[redacted]03-004	27	Open label, randomized	0.75 2xmonth (38) 1.5 1xmonth (36) Total N=74	6 months	Naïve patients only

After completion of 002 or 004, patients could enter extension study [redacted]03-003. At the time of the submission 34 patients from 002 were included in the study report of [redacted]03-003. A total of 61 patients from 004 were enrolled in the extension study; their results are not included in the submission.

Filing Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Clinical Pharmacology and Biopharmaceutics

Date: 19-JUL-99
From: Robert M. Shore, Pharm.D.
Through: Hae-Young Ahn, Ph.D., Team Leader
To: Crystal King, CSO
Re: Nutropin Depot (rhGH [rDNA origin] for injectable suspension)
NDA 21-075 / N-000
Genentech, Inc.

SYNOPSIS:

Nutropin Depot is a sustained release form of rhGH supplied as 13.5, 18, and 22.5 mg single-use vials. The formulation consists of micronized particles of rhGH embedded in a biodegradable poly D/L-lactide-co-glycolide (PLG) matrix which has been used in another depot product.. It is suspended in aqueous Diluent for Nutropin Depot (supplied in Nutropin Depot kit), the volume of which depends on the vial size; the resulting suspension is 19 mg/mL for each vial (2A, labeling, page 15). The proposed dosage is 1.5 mg/kg SC once each month or 0.75 mg/kg SC twice each month. The sponsor claims bioactive rhGH is released from the microspheres initially by diffusion followed by both diffusion and polymer degradation, with the polymer undergoing hydrolysis to lactic and glycolic acid and ultimately to cardon dioxide and water (3e, page 1). The sponsor's proposed indication for Nutropin Depot is the long-term treatment of growth failure due to lack of adequate endogenous growth hormone secretion (2A, labeling, page 9).

Drug product vial (3C, page 15):

Quantitative Composition Including Overage

Ingredient	Specification	Microsphere Composition[c]	Quantitative Composition per Dosage Unit[a]		
			13.5 mg rhGH	18 mg rhGH	22.5 mg rhGH
rhGH	NC[b]				
Zinc Acetate	USP				
Zinc Carbonate	NC[b]				
PLG	NC[b]				

[a] Nutropin Depot Final Product is supplied as 13.5, 18, and 22.5 mg dosage units; vials are overfilled to ensure delivery of labeled amount of somatropin.

[b] NC = Noncompendial; specification sheet provided in Section 4.A.3.a.

[c] Nutropin Depot Microsphere composition, % (w/w).

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ON ORIGINAL

ND.

Diluent vial (3C, page 16):

Quantitative Composition

Component	Compendial Reference	Amount/mL
Carboxymethylcellulose sodium, low viscosity	USP	30.0 mg
Polysorbate 20	USP	1.0 mg
Sodium chloride	USP	9.0 mg
Water for Injection	USP	q.s.

Nutropin Depot is not currently marketed in any country. Lyophilized Nutropin is approved for treatment of 1) growth failure due to lack of endogenous growth hormone, 2) growth failure associated with chronic renal insufficiency, 3) short stature associated with Turner syndrome and 4) adult growth hormone deficiency (AGHD).

Genentech is responsible for manufacturing the rhGH as well as labeling, packaging, final release and distribution of Nutropin Depot final vial product and the kit, and is responsible for manufacturing and testing the Nutropin Depot final product microspheres (3C, page 16).

This NDA is paper and electronic. The Human Pharmacokinetics Section (Section 6) is contained in volumes 1.1 to 1.5.

Three principal studies are discussed in this NDA: a Phase I safety and pharmacokinetic study in GHD adults (03-001), a dose ranging Phase I/II pharmacokinetic study in GHD children (03-002), and a Phase III efficacy study (03-004) with limited pharmacokinetics in GHD children. In addition, an extension study (03-003) for long term follow up is briefly included. Only one formulation was used in these studies, although lots produced at different scales of manufacture were used (3e, page 1).

03-001, a single-dose study, assessed the pharmacokinetics of hGH as well as its safety in adults with growth hormone deficiency. The pharmacokinetic portion of the study characterized the initial hGH release phase of 24–48 hours duration and the sustained release phase extending to 56 days from administration. Safety was evaluated by laboratory profiles, measurement of fasting and postprandial glucose and insulin levels, glycosylated hemoglobins, IGF-1, IGFBP-3, and antibodies to growth hormone, as well as assessment of clinical adverse events. According to the sponsor, this Phase I study in GHD adults showed that a single dose of Nutropin Depot elicited initial high hGH concentrations followed by sustained levels of both hGH and IGF-I for approximately 3 to 4 weeks postdose (3e, page 4-5).

Based on the hGH serum profile, IGF-I response and tolerability data from Study 03-001, 0.75 mg/kg every 4 weeks (0.75q4) was chosen as the initial dose for the Phase I/II efficacy and safety study in pediatric GHD subjects (Study 03-002). Following the 3-month data evaluation, 2 dose groups were added to Study 03-002: 1.5 mg/kg every 4 weeks (1.5q4) or 0.75 mg/kg every 2 weeks (0.75q2). The objective of this Phase I/II study was to evaluate the safety and efficacy of Nutropin Depot in children with repeated dosing up to 24 weeks. The study investigated previously–treated subjects and naive subjects. A subset of subjects was intensively sampled after the first or second dose of Nutropin Depot to characterize PK and PD (IGF-1, GHBP, IGFBP-3). (3e, page 5-6). According to the sponsor, a single dose of Nutropin Depot produced initially high hGH concentrations followed by a sustained elevation of both hGH and IGF-I levels which lasted between 2 and 3 weeks in GHD children. Overall, hGH, IGF-I, GHBP, and IGFBP-3 levels following Nutropin Depot SC administration in GHD children were reproducible at each cycle, and there was no evidence for progressive accumulation during the course of the study period. The rhGH was released from Nutropin Depot in a generally dose-proportional manner. Previous rhGH history (previously treated vs. naive) had no effect on the hGH pharmacokinetic profile after Nutropin Depot administration. The presence of anti-hGH antibodies in the serum had no apparent effect on any measured pharmacokinetic and pharmacodynamic parameter (3e, page 9).

03-004 was a Phase III, multicenter, open-label, 6-month study designed to demonstrate the safety and efficacy of two doses of Nutropin Depot in the treatment of children with growth failure due to GHD. Seventy-four prepubertal subjects with GHD who had not been previously treated with GH (naive) were enrolled and treated at 27 medical centers. Subjects were randomized centrally to one of the following two treatment groups: 1.5 mg/kg Nutropin Depot administered once a month or 0.75 mg/kg Nutropin Depot administered twice a month (3e, page 11). According to the sponsor, there was no significant increase in trough hGH and IGF-I, IGFBP-3 levels for the 1.5q4 group. For the 0.75q2 group, the trough level of hGH at Month 3 was increased from the baseline value but the level did not change significantly from Month 3 to Month 6, indicating no progressive drug accumulation. With the exception of the IGF-I level in the 0.75q2 group at Month 3, IGF-I and IGFBP-3 levels at Months 3 and 6 for all 3 dose groups were not apparently different from those at baseline supporting no accumulation in pharmacodynamic marker levels (3e, page 11).

03-003 is an ongoing, multicenter, open-label pediatric study designed to evaluate the long-term safety and efficacy of Nutropin Depot. 03-003 is being conducted as an extension to Studies 03-002 and 03-004. According to the sponsor, trough levels for hGH, IGF-1, and IGFBP-3 drawn predose at the clinic visits every 3 months showed a return to near predosing levels for both dose groups (3e, page 12).

The sponsor did not conduct an absolute bioavailability study. Instead, the relative bioavailability of single SC doses of Nutropin Depot based on comparisons with historical data from Genentech studies in normal adult males that received rhGH formulated for daily administration as a single SC bolus was estimated to be 44% in adults and 33%-38% in children. The estimated absolute bioavailability of Nutropin Depot was approximately 36% in adults and 27%-32% in children as compared to 83% for Nutropin AQ. The relative bioavailability after chronic treatment was also determined using an hGH AUC adjusted for chronic dosing per Kearns et al. 1991. These authors found an approximate 30% decrease in serum hGH AUC following 4-6 weeks of daily dosing (0.043 mg/kg/day). This AUC adjusted for chronic dosing may be a more representative reference AUC. When compared to the AUC value adjusted for chronic dosing, the relative bioavailability of Nutropin Depot was 63% in adults and 48%-55% in children (3e, page 12).

Multiple-dose simulations were performed to compare hGH observed serum profiles and predicted profiles of Nutropin Depot over a 6-month period in gHD adults and children. The sponsor claims that, overall, the simulated concentrations are in agreement with the observed data for children (6b, page 25).

The submission includes validation data for all assays (6d).

The sponsor has proposed two quality control dissolution release specifications: and The spec is rhGH release at hours and the spec is at hours. The sponsor is proposing month expiration dating (4a3f2, page 192).

The commercial manufacturing scale will be of microspheres; lots of this size were used in studies 03-002, 03-003 and 03-004 (3C, page 34; 6A, page 11).

RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has evaluated NDA 21-075/N-000 dated 25-JUN-99 for filing. Based on this review, DPE-2 has determined that the application is fileable. Comments should be forwarded to the sponsor as appropriate.

COMMENTS TO BE SENT TO MEDICAL OFFICER:

ND

1. Since the actual volume of reconstituted Nutropin Depot to be administered to each patient will depend on the patient's weight, perhaps one of the package inserts should include tables as follows:

Patient weight (kg):	Total amount of rhGH needed for 0.75 mg/kg dose:	Inject this volume of reconstituted Nutropin Depot for 0.75 mg/kg dose:
10	7.5	0.4
15	11.25	0.6
20	15	0.8
25	18.75	1.0
30	22.5	1.2
35	26.25	1.4
40	30	1.6
45	33.75	1.8
50	37.5	2.0
55	41.25	2.2

Patient weight (kg):	Total amount of rhGH needed for 1.5 mg/kg dose:	Inject this volume of reconstituted Nutropin Depot for 1.5 mg/kg dose:
10	15	0.8
15	22.5	1.2
20	30	1.6
25	37.5	2.0
30	45	2.4
35	52.5	2.8
40	60	3.2
45	67.5	3.6
50	75	3.9
55	82.5	4.3

This will also help the physician calculate the appropriate number of vials needed for each dose.

COMMENTS TO BE SENT TO SPONSOR:

1. Although an annotated PI is included in the electronic document as a PDF file and the sponsor has also included a Word file of the proposed labeling, this reviewer would find it more useful if the sponsor could submit one PI in Word format with clear indications of what is currently approved for Nutropin NDA 19-676 (e.g., regular text) and what are proposed changes (e.g., highlighted or colored text). This would expedite the review writing process.

2. The sponsor should provide intra/inter-assay precision and accuracy data from the actual assay runs conducted on IGF-1. This submission includes only the kit insert but this does not allow an evaluation of the assay's performance during actual analysis of samples from the clinical studies. Also, the sponsor should submit accuracy data for the GHBP assay. If this information is available in the submission, please indicate where it can be found.

CC: NDA 21-075/N-000 (orig., 1 copy), HFD-510(King, Perlstein, Berlin, Hertig), HFD-870(Ahn, ChenME), HFD-850(Lesko, Huang), CDR (Barbara Murphy)

STUDY SUMMARY

Summary Study Design for Nutropin Depot ([redacted] rhGH) Clinical Pharmacokinetic Studies

Study	Group	N (m/f)	Mean (Range) Age (yrs)	Mean (Range) BW (kg)	Dose (mg/kg)	Schedule	Sample Observations	Timepoints
[redacted]03-001	1	13 (8/5)	48 (27-67)[a]	88 (65-132)	0.75	Single	hGH, IGF-I, GHBP, IGFBP-2, IGFBP-3	Every 2 hours for 0-48 hours, twice a week for Days 2-27, and Days 41, 55
[redacted]03-002	1	Naive 9 (7/2) CT 10 (8/2)	9.3 (2.7-13.7) 9.3 (8.1-11.2)	23.2 (11.3-35.3) 29.1 (20.6-46.7)	0.75	Multiple, once every 4 weeks for 6 months	hGH, IGF-I, GHBP, IGFBP-3	Days 1, 7, 14, 21, 28 after each dose
	Subset[b]	13 (10/3) Naive 6 CT 7	9.7 (2.7-13.7)	27.6 (11.3-46.7)	0.75	After first or second dose[c]	hGH, IGF-I	Every 6 hours for 0-48 hours, twice a week for Days 2-28
	2	Naive 8 (5/3) CT 17 (11/6)	6.3 (3.6-11.4) 9.9 (7.3-14.1)	15.6 (11.7-23) 28.2 (17.4-43.6)	1.5	Multiple, once every 4 weeks for 6 months	hGH, IGF-I, GHBP, IGFBP-3	Days 1, 7, 14, 21, 28 after each dose
	Subset[b]	9 (3/6) Naive 6 CT 3	7.5 (3.6-14.1)	20.0 (11.7-36.4)	1.5	After first dose	hGH, IGF-I	Every 6 hours for 0-48 hours, twice a week for Days 2-28
	3	Naive 9 (7/2) CT 11 (6/5)	7.4 (5.5-11.1) 9.4 (4.3-13)	17.6 (14-26) 30.3 (14-69.2)	0.75	Multiple, once every 2 weeks for 6 months	hGH, IGF-I, GHBP, IGFBP-3	Days 1, 7, 14 after each dose

Summary Study Design for Nutropin Depot (rhGH) Clinical Pharmacokinetic Studies

Study	Group	N (M/F)	Mean (Range) Age (yrs)	Mean (Range) BW (kg)	Dose (mg/kg)	Schedule	Sample Observations	Timepoints
03-004	1	Naive 38 (21/16)	7.3 (1.6-12.2)[a]	18.3 (5.9-34.2)	1.5	Multiple, once every month for 6 months	hGH, IGF-I, GHBP, IGFBP-3	Baseline, trough levels at Month 3 and Month 6
	2	Naive 38 (21/16)	7.6 (3.2-11.9)	20.1 (8.8-43)	0.75	Multiple, twice every month for 6 months	hGH, IGF-I, GHBP, IGFBP-3	Baseline, trough levels at Month 3 and Month 6
03-003	1	Naive & CT 10 (9/1)	9.3 (2.7-13.7)	24.9 (11.3-35.3)	0.75	Multiple, once every month for 6 months	hGH, IGF-I, GHBP, IGFBP-3	Baseline, trough levels every 3 months
	2	Naive 12 (7/5)	7.8 (3.6-11.4)	20.1 (11.7-32)	1.5	Multiple, once every month for 6 months	hGH, IGF-I, GHBP, IGFBP-3	Baseline, trough levels every 3 months
	3	Naive 12 (9/3)	7.4 (4.5-11.1)	17.8 (14-26.5)	0.75	Multiple, twice every month for 6 months	hGH, IGF-I, GHBP,IGFBP-3	Baseline, trough levels every 3 months

M/F = Male/female.

Naive = Subjects not previously treated with hGH.

CT = Subjects previously treated with daily hGH administration before enrollment for this study.

[a] Mean (min-max) values.

[b] Subjects assigned to intensively sampled groups after a first or second dose in multiple dose regimens.

[c] The second dose data were used in the analyses for subjects that received their first dose of Nutropin Depot using dextran diluent because of incomplete dose administration with this diluent.

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14 Page(s) Redacted

Draft

Labeling

Meeting Minutes

IND # and Drug Name:	IND [redacted] [redacted] hGH
Meeting Date:	December 7, 1998
Time:	2:00 pm
Location:	Parklawn Conference Room "Potomac"
Indication:	Growth Failure due to GH deficiency (children)
Sponsor:	[redacted] Genentech
Type of Meeting:	Pre-NDA
Meeting Facilitator:	Saul Malozowski, M.D.
Sponsor Participant Lead:	Kenneth Attie, M.D.
Regulatory Project Manager:	Crystal King, P.D., M.G.A.
FDA Participants:	Saul Malozowski, M.D., Medical Team Leader (Acting) Robert Perlstein, M.D., Medical Officer Stephen Moore, Ph.D., Chemistry Team Leader (CMC only) William Berlin, Ph.D., Chemistry Reviewer Ronald Steigerwalt, Ph.D., Pharmacology Team Leader Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader Robert Shore, Pharm.D., Biopharmaceutics Reviewer Joy Mele, M.S., Statistician David Hussong, Ph.D., Microbiology Reviewer (CMC only)
Sponsor Participants:	[redacted] Senior VP, Medical & Regulatory Affairs [redacted] VP, Regulatory Affairs [redacted] Director, Biostatistics & Data Management [redacted] VP, Pharmaceutical Development [redacted] Director, Clinical Operations [redacted] Director, Pharmacokinetics [redacted] Clinical Consultant [redacted] Associate Director, Regulatory Affairs [redacted] Robert Garnick, Ph.D., VP, Regulatory Affairs (GEN) Kenneth Attie, M.D., Clinical Scientist, Medical Affairs (GEN) Allene Dodge, Director, Regulatory Affairs (GEN) Jeff Cleland, Ph.D., Senior Scientist, Pharmaceutical R&D (GEN) Timothy J. Breen, Ph.D., Associate Director, Biostatistics (GEN) Melinda Marian, M.S., Scientist, Pharmacokinetics and Metabolism (GEN) Bernice Welles, M.D., Director, Endocrinology and Neurology (GEN) Fiona Cameron, Senior Manager, Regulatory Affairs (GEN)

IND [redacted]

December 7, 1998

Meeting Objective:

To discuss the New Drug Application (NDA) for Nutropin Depot™ (also referred to as [redacted] rhGH) which is targeted for submission early first quarter of 1999. To present the clinical data and obtain agreement that the data support filing of the Nutropin Depot NDA for the long-term treatment of growth failure due to a lack of adequate endogenous growth hormone secretion in pediatric patients.

Background:

This is a follow-up to the October 28, 1997 end of Phase 2 meeting. The Phase 3 study is now complete and the NDA is targeted for first quarter 1999 submission.

Preliminary Agenda:

Prior to consideration by the Division of the Agenda questions as submitted, the sponsor reviewed the clinical trial results, the pharmacokinetic results, the proposed ISS/ISE analysis plan , the proposed safety update, and gave an overview of the planned electronic submission.

Action Items: Reviewers having requests for any hyperlinks should forward the same to the sponsor through Dr. King.

Agenda Item 1: Does the Agency concur that the safety and efficacy data support the filing of the Nutropin Depot NDA for this indication (long-term treatment of growth failure due to a lack of adequate endogenous growth hormone secretion)?

Response: An exhaustive pre-review of the data has not been performed; however, the following comments are offered: This indication appears to be acceptable.

Action Items: None.

Agenda Item 2: We are seeking approval for the two dose regimens used in the Phase 3 study. Does the Division agree that the data support both the 0.75mg/kg twice monthly and 1.5 mg/kg once monthly dose regimens?

Response: The data appears to support both; however, we will need to review further.

Action Items: None.

Agenda Item 3: Are the proposed integrated summary analysis plans acceptable?

Response: We would like to see the use of historical controls clarified. Also, please provide individual data for growth velocity before and during therapy, graphs of the same, and percent change in height. These should all be compared to normal growth curves.

The requested historical data is for comparative purposes. The individual data could be from clinical trials or post-marketing data.

Comments: The sponsor prefers to use standard height changes (as compared to normal) instead of percent change in height. In response to the question, "Would it be acceptable to pool two groups in Phase 3?" Ms. Mele indicated that she would need to examine the data.

Agreements: Dr. Attie confirmed that the data will be kept separate and not pooled for the labeling. This is acceptable.

Action Items: None.

Agenda Item 4: Is the proposed safety update, to be provided 4 months after the initial filing, acceptable?

Response: Yes.

Action Items: None.

Agenda Item 5: A demonstration of the CANDA and training regarding its use can be provided at a later date. Would the reviewers like to take advantage of this?

Response: As most of the reviewers have experience with electronic submission, we would most likely only need demonstration of any special features. Most importantly, we would like a specific contact person(s) to be available for questions/assistance.

Action Items: None.

Further Comments/Discussion/Action:

- Dr. Malozowski questioned how the sponsor planned to address in the label the issue that this formulation appears to be less efficacious than the traditional formulation. Dr. Attie indicated that the efficacy would be well described in the package insert; also there appears to be no risk that subjects would lose ground per growth.
- Ms. Marian clarified that for historical data, only the PK data is single-dose and is all in adult males. They do not have PK in the comparative population nor do they have multi-dose data; there is, however, single-dose pediatric PK data for [redacted]

  Action Item: **Ms. Marian** will send the projections.
- Dr. Shore requested that a comparative study be included in the NDA of Nutropin vs. the Depot to characterize the bioavailability.

  Dr. Shore indicated that the PKs are similar in adults and children, so that single, adult data could be used to compare the bioavailability.

Dr. Ahn stated that it is required to submit bioavailability for IV solutions, but that probably a bridging study for comparison would be sufficient. She then pointed out that: (1) single dose can't be compared without extrapolating based on 28 days, but it is not multi-dose data; (2) for absolute bioavailability, if IV can't be done, the sponsor could calculate one hundred percent bioavailability based upon release and them compare that to the observed.

- Dr. Ahn requested that computer-simulated repeated dose plasma profiles be provided over a six-month period from a single-dose study for adults. She commented that it is desirable for observed plasma levels for children be included in simulated profiles.
- Dr. Shore commented that the index provided for human PK studies does not indicate early Phase 1 or Phase 2 studies. Dr. Benziger provided a revised draft Table of Contents with expanded information.
- Dr. Ahn referred to the 10/25/98 submission of 13.5 vs. 22.5 mg. In order to waive bioavailability for the 13.5mg, she noted that we would need documentation of no differences for injection volume and concentration. The sponsor's own data or literature information could be used. This is due to possible differences in absorption from the different concentrations.

  Dr. Cleland indicated that all vial sizes would have the same concentration (19 mcg/ml). Ms. Marian indicated that she has literature data and will look at concentration and volume.

  Agreement: The historical approach discussed will be adequate.
- The Division requested sequential IGFs determination and time elapsed from last injection be provided. The sponsor indicated that this data is available as part of the PD markers.
- Dr. Malozowski requested that the allergic rash reaction be addressed in the label. The sponsor indicated that this would be described.
- Neither the Division nor the sponsor anticipated the need for an Advisory Committee meeting.
- Ms. Dodge asked about the timeline for implementation of the Financial Disclosure regulation.

  Action Item: **Dr. King** will inquire.
- Ms. Dodge inquired as to the possibility that a late February, 1999, submission would be reviewed within a ten-month time frame. Although Dr. Malozowski indicated the Division would certainly attempt to achieve this, a commitment could not be made due to impact of workload, etc. Dr. King suggested that the likelihood of a ten-month review would be enhanced with an earlier January submission.

IND [redacted]

December 7, 1998

CMC Breakout Section

Following the general discussion, Drs. Moore, Berlin, Ahn, Hussong, and King participated in a Chemistry, Manufacturing, and Controls meeting. Sponsor participants included Drs. [redacted] and Garnick, Mr. Blum, and Ms. Smith.

Agenda Item 1: Ms. Smith reviewed the content and format of the CMC section. She also provided an update of the manufacturing and regulatory timelines. The 22.5mg/vial configuration will now be the high level, not the [redacted] mg/vial as previously discussed. Stability will be updated prior to approval, approximately in September.

Comments: Dr. Berlin requested that a table be provided in the NDA to correlate all pre-clinical and clinical trial material to manufacturing scale and method.

Action Item: **Reviewers** are requested to provide feedback regarding desired links for the electronic submission.

Agenda Item 2: Dr. [redacted] reviewed the key elements of the proposed comparability protocols for post-approval manufacturing changes.

Comments: Dr. Moore disagreed with the firm's assertion that the five-fold scale-up of the microsphere process was a "changes being effected" category. He indicated that this is a critical step that may affect drug product release characteristics; therefore, it was most likely a "prior approval" category. The firm responded that they had successfully performed a larger fold scale-up previously during the development stage. Dr. Moore recommended that the information on the parameters examined, criteria and results may be provided in the NDA to support their assertion. The Agency will determine the reporting category at the time of NDA approval.

Dr. Berlin suggested that the main section be written like a "supplement with blank data tables".

Dr. Moore noted that more than one lot may need to be examined to insure that the product was within the normal variance. Additionally, a written commitment should be added to the list of items the firm proposed to include in their comparability protocol.

Dr. Ahn mentioned that a human bioavailability study was not needed for lot-to-lot variability. However, if five-fold scale-up is an issue, bioavailability for scale up may be necessary, and the Agency will have an internal discussion.

Agenda Item 3: Dr. [redacted] provided an overview of the diluent for Nutropin Depot. [redacted] will submit a DMF by the end of 1998. This will be cross-referenced by the Depot NDA.

Comments: Dr. Berlin commented that sterility-related items, appearance, and particulates of the diluent would need to be monitored on stability.

IND [redacted]

December 7, 1998

Action Item: [redacted] will send in the stability protocol.

Additional Items for Consideration:

- Dr. [redacted] inquired if it would be acceptable to do only the [redacted] assay. Dr. Ahn responded that this would not be acceptable.
- Dr. [redacted] suggested a [redacted] and a [redacted] assay and not to do intermediate points on the [redacted] assay. Dr. Ahn will consider this.

Action Item: **Dr. Ahn** will research whether intermediate points are required.

Prepared by: /S/ 12/22/98, Regulatory Project Manager
Crystal King, P.D., M.G.A. Date

Concurrence: /S/ 1/4/99, Meeting Facilitator
Saul Malozowski, M.D. Date

/S/ 12/22/98, CMC Breakout Lead
Stephen Moore, Ph.D. Date

Concurrence:	Sol Sobel, M.D., Division Director		12/16/98
	Robert Perlstein, M.D., Medical Officer	NCR by	12/22/98
	William Berlin, Ph.D., Chemistry Reviewer		12/15/98
	Ronald Steigerwalt, Ph.D., Pharmacology Team Leader		12/16/98
	Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader		12/22/98
	Robert Shore, Pharm.D., Biopharmaceutics Reviewer		12/22/98
	Joy Mele, M.S., Statistician		12/17/98
	David Hussong, Ph.D., Microbiology Reviewer		12/17/98

Meeting Minutes

IND# and Drug Name:	IND [redacted] [redacted] hGH
Meeting Date:	August 25, 1998
Time:	11:00 am
Location:	Parklawn Conference Room "P"
Indication:	Growth Failure due to GH deficiency (children)
Sponsor:	[redacted]/Genentech
Type of Meeting:	Pre NDA/Chemistry
Sponsor Participant Lead:	[redacted] Ph.D.
Project Manager:	Crystal King, P.D., M.G.A.
FDA Participants:	William Berlin, Ph.D., Chemistry Reviewer David Hussong, Ph.D., Microbiology Reviewer Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader
Sponsor Participants:	[redacted] Vice President of Regulatory Affairs [redacted] [redacted] Vice President, Operations [redacted] [redacted] Associate Director, Regulatory Affairs [redacted] [redacted] Associate Director, Formulation Development [redacted] [redacted] Director, Quality Control [redacted] Pamela Higgins, Senior Regulatory Affairs Associate (GNE) Jack Regan, Director, Pharmaceutical Manufacturing (GNE) Art Blum, Director, Regulatory Affairs (GNE) Bob Baird, Director, Validation and Technical Support (GNE) Elizabeth Smith, Manager, Regulatory Affairs (GNE) Ed Cox, Manager, Quality Control Stability (GNE)

Meeting Objective:

1. Discuss the stability program and proposed dating periods for process intermediates and final product.
2. Provide an update on sterility assurance.

Background:

[redacted] is a sustained -release injection of rGH. This meeting is a follow up to the 1/28/98 meeting at which FDA requested further validation and sterility information prior to the NDA submission. Testing is expected to commence late October; the NDA to be filed the end of December, 1998. The marketed name for [redacted] hGH will be Nutropin Depot.

UPDATE SINCE JANUARY 28, 1998, MEETING

Agenda Item 1: Is the proposal for potency testing of [redacted] hGH acceptable?

Agreements:

1. The percent SEC may be reported for routine release of the final product without further calculation. (Dr. Berlin)
2. The [redacted] assay will be performed for bulk microspheres and will be repeated on the final product and on the first three validation lots. (Dr. Berlin)

Unresolved Issues: None

Action Items: None

Agenda Item 2: Is the plan for the [redacted] assay acceptable?

Agreements:

1. The *in vitro/in vivo* correlation is not necessary since human data is not being used for a PK perspective. However, the sponsor may wish to perform such a correlation with human data at some future point. This might substitute for bioequivalence studies or be useful for various changes, such as formulation, facilities, etc. (Dr. Ahn)
2. The sponsor will run both [redacted] and [redacted] for the release testing. (Dr. Ahn)
3. The [redacted] test must show an [redacted] within [redacted] hours with at least two data points. (Dr. Ahn)
4. The stability data will show one assay to correlate with the rat data. (Dr. Berlin)

Unresolved Issues: Phase 3 testing will determine monthly or twice monthly dosing.

Action Items:

1. Dr. Ahn will review and comment on the *in vitro* data submitted on July 27, 1998.
2. [redacted] will submit correlation data to Dr. Berlin.
3. Dr. Berlin will further review the stability data in order to determine that only the [redacted] assay is sufficient.

MICROBIOLOGY DISCUSSION TOPICS

Agenda Item 3: Are the plans for [redacted] simulations acceptable?

Agreements:

1. The plans appear to be acceptable. However, for validating sterilization of poor [redacted] surfaces, such as stoppers, [redacted] should be performed instead of utilizing [redacted] (Dr. Hussong).

Unresolved Issues: None

Action Items: None

Agenda Item 4: Is the microbiological testing presented acceptable?

Agreements:

1. The testing is acceptable for the drug component. The diluent will be tested for sterility after [redacted] sterilization. (Dr. Hussong)

Unresolved Issues: None

Action Items: None

Agenda Item 5: Does the overall validation approach meets Agency expectations?

Agreements:

1. The overall validation approach appears to meet Agency expectations. (Dr. Hussong)

Unresolved Issues: None

Action Items: None

STABILITY DISCUSSION TOPICS

Agenda Item 6: Are the proposed expiration dating for [redacted] hGH bulk drug substance, intermediates and final product acceptable?

Agreements:

1. The dating for the final product can probably go to [redacted] months, with sufficient data. (Dr. Berlin)
2. Stability studies will continue. [redacted] will submit updates and requets for extended dating approximately six months after the NDA is filed. (Dr. [redacted]

Unresolved Issues: None

Action Items: None

Agenda Item 7: Are the proposed stability protocols for the qualification lots acceptable?

Agreements:

1. The protocols for the bulk drug, zinc acetate, bulk microspheres, and final product appear to be acceptable. (Dr. Berlin)

Unresolved Issues:

1. The sponsor proposed three dose strengths: 22.5 mg, 18 mg, and probably 13 mg. Only 22.5 mg has been studied in PK and clinical studies. There may be an issue on different injection volumes. (Dr. Ahn)

Action Items:

1. Dr. Berlin will consult the chemistry team regarding the use of filling levels for validation and stability.
2. Dr. Hussong will determine whether container closure integrity validation should be performed annually or otherwise.
3. Dr. Ahn will consider the PK issues; Dr [redacted] will send Dr. Ahn additional information and tables.

Summary of Action Items: There are five Action Items listed above.

Prepared by: /S/
Crystal King, P.D., M.G.A., Project Manager 9/02/98

Concurrence: William Berlin, Ph.D., Chemistry Reviewer 9/02/98
Hae-Young Ahn, Biopharmaceutics Team Leader 9/08/98
David Hussong, Ph.D., Microbiology Reviewer 9/10/98

APPEARS THIS WAY
ON ORIGINAL

JOHNSTON

IND [redacted]

MEETING MINUTES

Meeting Date: January 29, 1998 9:30 AM (Meeting Concluded at 10:35 AM)

Drug: [redacted] hGH

Indication: GH Deficiency Sponsor: [redacted] /Genentech

Meeting Type: Pre-NDA Chemistry

Attendance: M. Johnston, CSO (recorder) W. Berlin, Ph.D. (Chemist)
S. Moore, Ph.D., Chemistry Tm. Ldr.
P. Cooney, Ph.D. (HFD-160/Microbiology)
D. Hussong, Ph.D. (HFD-160/Microbiology)

Attendance (Sponsor): See Attachment #1

Meeting Objectives:
1. Review of [redacted] hGH Manufacturing Process
2. Review of [redacted] hGH Specifications and Testing
3. Review of Process Validation and Sterility Assurance
4. Review of Product Comparability

I. INTRODUCTIONS: Dr. [redacted] started by thanking FDA for the meeting and introductions went "around the table." He then reviewed the meeting agenda.

II. Mr. [redacted] then presented a brief overview of the project and the six topic areas (as per the pre-meeting package dated January 12, 1998):

1. Definition of the Test Article for Routing Release Testing
   Question: Is this proposal acceptable to the agency?
   Answer: Yes, with the following qualifications:
   A. For NDA organization of information:
      Specifications Sheet (microsphere vs. Final vials)
   B. Potency [redacted] possible in future with validation):
      Should be performed on final vials
   C. Explain rationale for division of tests performed on microspheres vs. final vials

2. Proposal for Selecting an [redacted] Assay
   Question: In selecting an [redacted] assay, are both and in vivo/in vitro correlation and release of [redacted] of the protein required?
   Answer: Deferred to Biopharm
   ACTION ITEM: [redacted] will send in a biopharm submission for review on this topic