CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

BLA 125103/0

Chemistry Review(s)

Palifermin CMC REVIEW

Product Review Data Sheet

The CMC Executive Summary

I. Recommendations

The Division of Therapeutic Proteins, OBP, OPS, CDER recommends approval of BLA #125103, and the Post-Marketing Commitments as discussed below.

A. Recommendation and Conclusion on Approval

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of BLA #125103 for Palifermin manufactured by Amgen, Inc. Adequate documentation of this recombinant form of human Keratinocyte Growth Factor has been presented in respect to manufacturing controls, methods and process validation, product characterization (purity and product and non-product related impurities), consistency of manufacture (comparability of pilot, clinical and commercial forms of Palifermin and conformance batch lots), release and stability specifications, and real time and accelerated stability data.

B. Agreements reached with Amgen during BLA Review and Phase 4 (Post-Marketing) Commitments.

During the review cycle and after the Pre-approval Inspection of the Lake Center Facility in Colorado, negotiation with Amgen resulted in approximately 26 submissions (see Table of BLA Information Requests immediately below) which in summary tightened of the release and stability specifications and the control of manufacture. In addition, 6 PMCs were agreed upon as listed below which specified better control of manufacture, improvements in assay methodology and ensured continued review of product stability.

FDA recommended that Amgen address modifications to DS and DP specifications prior to licensure. Amgen has agreed to revisions of the release specifications for both DS and DP. The [ ] release specification for the [ ] was tightened from [ ], the [ ] tightened from [ ] and [ ] from [ ] (for DS, and > for DP) are all acceptable. In addition, the [ ] specification was changed from [ ] and the [ ] value from < [ ] E coli protein/ mg of Palifermin. Amgen has agreed to add [ ] as a drug product release specification and stability acceptance criteria with a limit of greater or equal to [ ] Following [ ] evaluation of [ ] Drug Product lots Amgen will revise the DP specification to equal the DS [ ] Specification of [ ]

In addition, an ELISA [ ] was agreed upon as a [ ] Test after more precisely defining the [ ] measurement and committing to examine the assay specificity in respect to other closely related members of the FGF family of growth factors. Additional [ ] In-Process Control steps were added, and [ ] criteria acceptable to DTP were established. For DS [ ] these are respectively, [ ] and no more than [ ] after the [ ] process [ ] Importantly, an action limit of [ ] and report of the actual [ ] result in any given final DS lot will now be included in the that lot's Certificate of Analysis. The palifermin in vitro bioassay [ ] will be used to calculate an effective concentration (ED50) for the currently qualified reference standard, lot [ ] Limits will be established by performing dose-response curves in a minimum of [ ] assays that include normal sources of laboratory variability. Amgen agreed to provide the [ ] reference standard ED50 control limits to the agency once established. A more quantitative definition of [ ]" for the [ ] Test was agreed upon that uses acceptable specified [ ] in respect to both retention times and [ ]

The summation of Amgen's response to 25 separate CDER Information Requests, as of December 7th, 2004 is shown below.

BLA Information Requests

Subject	Deliverables	Amendment Submitted	Module Links	Status
[ ]	[ ]	11/2/2004	3.2.S.3.1	Resolved
		11/2/2004	3.2.S.2.2, 3.2.S.2.3	Resolved
		11/10/2004	3.2.S.4.2	Resolved
		/10/2004	3.2.S.2.2	Resolved
		11/10/2004	3.2.S.4.5, 3.2.P.5.6 (Split into two documents DS and DP)	Resolved
		11/10/2004	3.2.S.2.2	Resolved
		11/10/2004	3.2.S.4.2, 3.2.R.1	Resolved
		11/2/2004	3.2.S.2.6, 3.2.S.3.1, 3.2.P.2.2, 3.2.P.2.3	Resolved
		11/10/2004	3.2.S.2.2, 3.2.S.2.6	Resolved
		11/10/2004	3.2.S.3.1	Resolved
		11/10/2004	3.2.S.3.2	Resolved
		11/10/2004	3.2.S.2.6	Resolved
		11/10/2004	3.2.S.2.5	Resolved
		11/10/2004	3.2.S.2.2	Resolved
		11/10/2004	3.2.A.1	Resolved
[ ]	[ ]	11/10/2004	3.2.S.2.2, 3.2.P.8.4	Resolved

1 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Each of the above changes in the manufacture and control of Palifermin DS and DP are further discussed in the body of this review as indicated in the Table of Contents.

CMC Post Marketing Agreements as of December 12th, 2004 are listed below. Amgen agrees to:

1. To re-evaluate the following:

a. Action and acceptance limits for Palifermin Drug Substance yields after manufacture of ~ lots;

b. In-process controls, release, and stability specifications on all Drug Product lots manufactured through the end of 2007; and

c. In-process controls, release, and stability specifications on all Drug Substance lots manufactured through the end of 2008.

2. Results of these re-evaluations will be submitted to the agency by March 31, 2008 for drug product and March 31, 2009 for drug substance.

3. To evaluate the photo stability of Palifermin Drug Product under conditions that are representative of the conditions for use of the lyophilized and reconstituted Palifermin Drug Product, and to submit the results of the study with revised labeling, if necessary, by September 30, 2005.

4. To evaluate the specificity of the ELISA [ ] Method as an identity test for the Palifermin Drug Product, by a quantitative comparison of cross-reactivity to a series of FGF-related growth factors that are highly homologous in amino acid sequence to Palifermin, and report the results of this study by December 31, 2005.

5. To establish an in-process control test [ ] in the manufacture of Palifermin Drug Substance by September 30, 2005.

6. To submit ED50 control limits for the reference standard used in the bioassay (A0742) to the FDA by September 30, 2005.

7. Stability PMC; To be provided by the agency. However, Amgen's wording of the proposal is: "To commit to provide, in an Annual Report of Minor Changes,stability data to support an extension of expiration dating period based on real time stability data as outlined in the Post-approval Stability Protocol and Stability Commitment (Sections 3.2.S.7.2 and 3.2.P.8.2)."

8. To evaluate, using the [ ] Test, [ ] Drug Product vials exposed to accelerated storage conditions including heat and light, and to report results of the study by September 30, 2005.

It is the summary view of the Division of Therapeutic Proteins (DTP), Office of Biotech Products, that the manufacture and control of Palifermin Drug Subtance and Drug Product provides a quality therapeutic. Palifermin BLA Amendments #'s 5, 9, 11, 15 and 17 specifically catalogue Amgen responses to Information Requests from DTP and are collectively listed (incorporating those above) and briefly described under Section #5 of the CMC Review Data Sheet below.

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Palifermin is the USAN name for Amgen's Keratinocyte Growth Factor-1 (KGF-1), a member of the Fibroblast Growth Factor Family within which KGF-1 is also known as FGF-7. Palifermin is manufactured via recombinant DNA technology in *E. coli*, [ ] drug substance (DS) that begins at the N-terminal amino acid #24 of native Human KGF. The Palifermin Drug Substance is [ ] as a lyophilized drug product (DP) for refrigerated storage.

Palifermin is an N-terminal 23 amino acid truncation of native human Keratinocyte Growth Factor that was discovered by Rubin et al and published in PNAS in 1989. KGF is a paracrine protein growth factor produced by mesenchymal cells, particularly sub-epithelial fibroblasts, and binds FGFR-4, which is a splice variant of FGFR IIIb expressed in many epithelial cells. After binding FGFR-4, KGF initiates epithelial cell proliferation, migration and up-regulates expression of numerous protective cell functions. As listed in the Palifermin Package Insert, native human KGF has trophic effects on many types of epithelial surfaces and tissues including tongue, buccal mucosa, esophagus, stomach, intestine, salivary gland, lung, liver, pancreas, kidney, bladder, mammary gland, and skin (hair follicles and sebaceous gland, and the lens of the eye. The KGF receptor is not present in cells of the hematopoietic lineage.

B. Description of How the Drug Product is Intended to be Used

At the bedside, Palifermin DP is reconstituted in WFI for IV bolus injection as an adjunctive treatment of adult hematological malignancies to mitigate mucositis attendant to myeloablative therapy with radiation and chemotherapy.

C. Basis for Approvability or Not-Approval Recommendation

Approvability is based on the submission of fully adequate Biochemistry, Manufacturing and Control documentation for this recombinant form of human Keratinocyte Growth Factor. This includes thorough information and data on manufacturing controls, methods and process validation, product characterization (purity and product and non-product related impurities), consistency of manufacture (comparability of

pilot, clinical and commercial lots of Palifermin), specifications, and stability data.

Palifermin is a highly purified and well-characterized product with release specifications that will ensure lot-to-lot consistency. The manufacturing process is under control and has been satisfactorily validated. The clinical and conformance lots of drug substance and drug product were comparable. The product has a high degree of stability in the liquid form, and the low extent instability of the lyophilized and reconstituted drug product has been carefully examined., and will remain within specifications if stored as recommended during the assigned shelf life of [ ] for drug substance and 18 months for lyophilized drug product.

Immunogenicity does not appear to be a concern for this product. Patients receiving repeated Palifermin treatment showed a low incidence of antibody detection without development of neutralizing antibodies. KGF is protein within the 22-member FGF family of growth factor; consequently, with this high redundancy, patients developing antibodies would not be expected to experience long term or severe side effects. In addition, patients under going chemotherapy and radiotherapy, as in the clinical indication of this Palifermin BLA, are immunologically compromised.

D. List of Deficiencies to be Communicated-

During negotiation with Amgen over the course of this BLA review, and after the Pre-Approval Inspection, a satisfactory resolution of all significant CMC issues that were identified was obtained. These included revised DS and DP Specifications, changed In-Process Controls, refined methods of reporting analytical results, etc which are described in detail in the body of this review.

Among the significant issues resolved were 1) the placement of [ ] action limit of [ ] for Palifermin Drug Substance and the actual test result in the DS Certificate of Analysis, 2) addition of a [ ] limit of [ ] to the in-process controls following filtration of the final bulk drug substance, 3) improved quantitation of the ELISA method of an DTP-recommended [ ] Test for the Palifermin Drug Product, 4) more exacting definition of [ ], and 5) others as detailed in the Post marketing Commitments enumerated above.

The 483 Observations during Pre-Approval Inspection are described in the EIR and will not be discussed in this CMC Review. Non-483 issues are discussed in Dr. Emily Shacter' PAI Report.

A. **Reviewer's Signatures:** **Kurt Stromberg, M.D.** 12/14/04
Ralph Bernstein, PhD 14dec04
Supervisor **Emily Shacter, PhD**

B. Endorsement
DTP, Director **Amy Rosenberg, M.D.** for A. Rosenberg 12-14-04

Project Manager Susan Giuliani 12/14/04

CMC Assessment

I. Review of the Common Technical Document-Quality (CTD-Q) Module 3.2: Body of Data

The Palifermin BLA was submitted in an electronic CTD form. The overall review and evaluation of Palifermin Product Quality follows the outline of the CMC Review Data Sheet.

The Sponsor information is in non-bold type (Arial Type) and the CMC reviewer comments follow in BOLD TYPE (Times New Roman Type) . Each major heading is summarized briefly prior to presentation of excerpts from the BLA.

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)- **see above**

B. Description of How the Drug Product is Intended to be Used-**see above**

C. Basis for Approvability or Not-Approval Recommendation

Palifermin is recommended for approval for approval based on a satisfactory level of drug quality in respect to Palifermin protein characterization (purity/impurity and potency), and consistency (comparability and stability) of both DS and DP. Please see the expanded statement on approval above.

D. List of Deficiencies to be Communicated –

a. See executive summary above.

a. Address 483 Observations of Inspection. This is a Div of Therapeutic Protein Facilities issue and will not be discussed in this CMC Review.

b. Non-483 Inspection Items. See Dr Emily Shacter's Inspection Report.

III. Administrative

A. Reviewer's Signatures **Kurt Stromberg, M.D.** 12/14/04

Ralph Bernstein, PhD

Supervisor Emily Shacter, PhD

B. Endorsement Block

DTP Division Director Amy Rosenberg, M.D. 12-14-04

Project Manager, Susan Giuliani 12/14/04

CMC Review Data Sheet

1. **BLA#** --STN #125103

2. **REVIEW #:**

3. **REVIEW DATE:** 15-Sep-2004, initial draft review

4. **REVIEWER:** Kurt Stromberg, M.D., Division of Therapeutic Proteins, OBP, OPS, CDER.

5. **PREVIOUS DOCUMENTS[1]:**

The IND preceding this BLA is [ ] was submitted in 1995 and currently is up to Amendment #232. The most relevant up-dated CMC amendment is #192, submitted electronically in January, 2004.

The following is a listing, in temporal sequence, of important memoranda, meeting minutes, and amendments to the BLA.

Previous Documents	Document Date[2]

Pre-BLA CMC meeting Letter of Dec.2, 2003:

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date:

From: Janet Condino, DRMP, HFM-588

To: BB-IND [ ]

Subject: Pre-BLA Meeting to Discuss CMC Section of BLA Submission

Meeting Date: December 2, 2003 **Time:** 3:00-4:30 pm

Location: WOC1/Conference Room 2

Meeting Requestor/Sponsor: Amgen, Incorporated

Product: Keratinocyte Growth Factor (human, recombinant, E. coli, Amgen)

Proposed Use: [redacted]

Type of meeting: Pre-BLA (CMC)

Meeting Purpose: To obtain agreement from the Agency on the proposed content and format of the CMC section (Modules 2 and 3) of the BLA in electronic CTD format that will be submitted for palifermin to support the proposed indication

Sponsor questions and FDA response:

Amgen seeks agreement that the proposed chemistry, manufacturing, and controls information to be included in the BLA will support registration of palifermin for the proposed indication, including:

1. *The manufacturing process has undergone changes during commercialization efforts. Amgen proposes that analytical compatibility data generated sufficiently demonstrates product comparability. Does the Agency agree?*

FDA Responses:

- Yes, by physico-chemical analysis the two products appear to be comparable. The Agency requests comparability studies on three (3) consecutive drug substance lots to demonstrate consistency of comparability and manufacture, particularly of the product-related variants and impurities by using the following assays: [redacted] Western blot immunoassays of [redacted] using [redacted] primary and secondary structure analysis by [redacted] analysis, and ELISA for [redacted] It was suggested that this analysis be done [redacted] the probability of detecting [redacted]

  Amgen response: The current assay used to detect [redacted] sensitive to — ppm. To this date, no [redacted] have been detected using this method.

- The Agency requests [redacted] studies to detect possible differences in product [redacted] on both the clinical scale drug product and the commercial scale drug product as formulated with [redacted]

Amgen response: Development of an appropriate analytical [ ] methodology has presented some difficulties. Would [ ] studies by [ ] be acceptable?

FDA response: Any validated methodology showing inter-lot comparison of the extent of product [ ] is acceptable. The ability of the assay to detect both [ ] should be demonstrated.

- In addition, please present data demonstrating that the proposed process-related changes associated with scale-up do not affect plasmid retention and genetic stability.

Amgen response: Data will be provided.

2. *For commercial product, does the Agency agree that Amgen's approach to setting specifications and proposed analytical methods are acceptable?*

FDA responses:

- No. It is necessary to designate provisional specifications beyond "Report" for [ ]

Amgen response: Specifications will be established.

- Agency question: What is your plan for designation of the Reference Standard for the DS and DP under commercial manufacture?

Amgen response: A new, [ ] based on a commercial scale production of DP has been developed by Amgen.

3. *Does the Agency agree that submitting analytical method summaries in the BLA are sufficient in place of full analytical method descriptions?*

FDA response:

- No. Electronic submission facilitates a more complete disclosure. In addition to these summaries, please include a detailed description of each analytical method (in particular, data on method and process validation). Line-by-line SOP information is not needed.

Amgen response: There is some uncertainty as to the amount of detail that the Agency expects.

FDA response: The summary information provided in the EOP2 package is not sufficiently detailed. A suggested guideline would be to provide summaries sufficiently detailed to allow conceptualization and critical analysis of the method. Validation data should also be provided.

4. *Does the Agency agree that the stability package to be included in the BLA and proposed stability updates to be made during the applicant's review are sufficient to support proposed expiry dating?*

FDA response:

- Yes, the stability package will support the proposed expiry of – months for the commercial bulk drug substance and – months for the commercial drug product by November, 2004. Evidence that stability-testing assays are, in fact, stability-indicating should be provided. Real-time and accelerated data under stressed conditions of increased temperature, moisture and light are expected.

Amgen response: Stability data will be updated during the course of the review as they become available, as well as evidence on the stability-indicating assays.

5. *Does the agency agree with the proposed organization of the CMC section of the application that will be submitted as an electronic BLA in CTD format? Are there any specific Agency requests regarding this format?*

FDA response:

- The general organization is fine. However, where will Assay Methodology and Validation for Immunogenicity be presented, as well as the clinical application of these assays to patient serum samples?

  Amgen response: Assay Methodology and Validation for Immunogenicity will be presented in the non-compendial methods section, Module 3.1.R.1.

6. *Amgen's LakeCentre manufacturing facility will not be in production during the anticipated time of the preapproval inspection. All manufacturing records will be available and the facility will be available to tour. Does the Agency concur that this will be sufficient to complete the inspection?*

FDA response:

- No, pre-approval inspections are customarily carried out during commercial manufacture. Alternatively, we will need to schedule the PAI during the

production of a product that utilized similar production processes.

A discussion ensued on alternative approaches to a mutually acceptable schedule for pre-approval inspection. FDA stated that inspection of a non-operational facility will not be acceptable and that pre-approval inspection must be carried out during commercial manufacture. [redacted]

[redacted] FDA requested that Amgen, (a) identify key unit operations and (b) put together a proposal for inspection of a [redacted] and submit it as an amendment to be reviewed by DMPQ.

7. *Does the Agency agree that sufficient information will be included in the BLA to establish the immunogenicity of palifermin. Are there any outstanding issues with regard to validation of immunogenicity assays used in palifermin clinical trials?*

The following response was presented during the meeting and subsequently FAX'ed to Amgen on December 12, 2003:

a. Please re-determine the [redacted] of the ECL immunogenicity assay. The agency suggests readjusting the [redacted]. In addition, please justify the use of [redacted] in generating the assay [redacted] as the values obtained from these different populations may be very different.

b. Please reassess the definition of a positive response induced by treatment based on the statistically justified variability of the assay.

c. Regarding assay validation, please address the following issues.

   1. The agency understands that proper performance and interpretation of data using the ECL [redacted] assay is highly dependent on [redacted] of the reagents used in this system. Please provide any relevant data generated during assay [redacted], including [redacted] and the impact of using different lots of [redacted].

   2. Please address whether [redacted] of palifermin has the potential to obscure critical determinants that could be recognized by antibodies generated in patients. Assessing the biological activity of these molecules in a bioassay provides assurance that the higher order structure of palifermin has not been adversely affected by the conjugations.

   3. Please provide data documenting the specificity of the ECL [redacted] assay. Such studies could include a demonstration that soluble palifermin, but not unrelated molecules, inhibit the assay. It is also of

interest to know if any KGF-related molecules have the capacity to interfere with the assay. In addition, please provide data addressing matrix-related interference.

4. You have documented the sensitivity of your assay using a polyclonal rabbit serum. Although not required by the Agency at this time, please provide any data you might have regarding the sensitivity of the assay obtained with antibodies of different affinities.

5. The LOD of the ECL [ ] assay needs to be reassessed. The agency suggests developing an LOD based upon the titration of the antibody in untreated patient serum, e.g., from page 5/12 of the KGF assay validation, the data suggest that approximately [ ] is an appropriate LOD.

6. Please provide additional data demonstrating assay robustness. Currently, only the impact of freeze/thawing of patient samples and varying lots of labeled palifermin have been examined.

d. Palifermin and/or endogenous KGF may interfere with the ability to detect anti- Palifermin or KGF antibodies.

1. Please provide data addressing the potential for palifermin or endogenous KGF to interfere with antibody detection

2. Please comment on the half-life of palifermin *in vivo*, and how it impacts the timing of sera sample acquisition.

e. The recommended design of the assay has the potential to detect false positives. To discriminate these potential false positives from true positive samples, please develop and implement a confirmatory immunodepletion/immunoadsorbtion assay into the current testing scheme.

f. The RIA, ELISA and ECL assays each use palifermin [ ] to detect anti-Palifermin antibodies. Please provide data addressing the ability of such antibodies to cross-react on and potentially neutralize endogenous, native KFG.

g. Reporting of patient immunogenicity data should be modified to reflect the sensitivity of the bioassay. The sensitivity of ECL [ ] assay is greater than that of the bioassay. Hence, samples reported as positive in the ECL [ ] assay but not reactive in the bioassay should be reported as "ECL [ ] assay positive, neutralizing capacity below limit of detection" since neutralizing antibodies at levels below [ ] can still have a physiological effect. These patients should continue to be monitored in any future trials.

h. After [ ] appropriately revalidating the assay, please retest patient samples that have previously been evaluated in RIA/ELISA assays.

i. Please provide the current plan regarding the banking and long term storage of patient serum samples.

j. Please address the appropriateness of discarding the ELISA assay and related results, especially in regard to the retesting of ELISA positive samples with ECL [ ] assay.

Additional Comments:

1. The briefing package indicated that the [ ] stoppers [ ] [ ] for clinical use and the — stoppers [ ] by Amgen) for commercial use are equivalent. Amgen will need to validate the [ ] of the stoppers and qualify the [ ] stoppers through [ ] process. Container/closure integrity studies should be reevaluated.

2. The clinical formulation [ ] used [ ] 5 cc vials and the commercial formulation [ ] will use [ ] 5 cc vials. Amgen states that the vials are identical dimensionally and meet the same requirements for [ ] glass and therefore they are very similar between the two sites. Please note that although both vials are [ ] glass, each vendor has a slightly different [ ] glass formulation. Stability studies will ultimately determine the equivalency of the vials.

3. [ ] studies will need to be revalidated since the commercial equipment uses different formulation [ ]

4. Shipping validation from LakeCentre to the contract — and from the contract [ ] to the distributor will need to be performed.

5. The lyophilization cycle for the commercial product is different from the cycle used for the clinical product. The commercial lyophilization process should be revalidated using at least three full scale lots. You may also decide to validate [ ] loads in addition to three full scale lots.
A discussion followed on the relative merits of validation with [ ] versus validation with a [ ] FDA stated that while the experience with a [ ] is useful, a [ ] is, in fact, a worse-case scenario.

Issues Requiring Further Discussion:

A decision was made to end discussion on the immunogenicity issues because Amgen felt that the appropriate sponsor representatives were not present at the meeting.

Action Items:

- Amgen will provide comparability data on three (3) consecutive drug substance lots to demonstrate consistency of manufacture and comparability
- A teleconference will be scheduled to discuss and resolve the immunogenicity issues
- Amgen will submit [ ] data on both the clinical scale drug product and the commercial scale drug product. FDA prefers [ ] analysis, but other validated methods may be acceptable.
- Amgen will provide data demonstrating that the process changes related to scale-up do not affect plasmid retention and genetic stability.
- Amgen will establish specifications for [ ] and *E. coli* [ ] for the bulk drug substance, and [ ] for the drug product.
- Amgen will submit more detailed analytical method descriptions including validation data.
- With respect to stability studies, Amgen will provide evidence that the planned stability assays are is stability-indicating. In addition, FDA expects real-time and accelerated stability data to be collected.
- As an approach to resolving the conflict between Amgen's construction plans for the LakeCentre manufacturing facility and the need for a pre-approval inspection, Amgen will submit a proposal and detailed plans for inspection [ ] or will provide dates when the facility will be in production of either palifermin or a product using a similar manufacturing process..
- Amgen will revalidate the commercial [ ] process using three (3) full-scale lots,

Amgen intends to submit the BLA in eCTD format with a request for priority review, during the second quarter, 2004.

FDA Attendees: Tony Mire-Sluis, Ralph Bernstein, Kurt Stromberg, Carolyn Renshaw, Janet Condino, Yuan-Yuan Chiu, Karen Jones, Jeanne Delasko, Emily Shacter, Patricia Dinndorf, Barbara Wilcox

Sponsor Attendees: Scott Buckel, Alessandra Cesano, Bruce Gardner, Richard Lit, Jian Ma, Patti Meyer, David Smiley, Kathleen Sniff, Dean Waters

Filing Review Letter at 45 days:

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: August 11, 2004

From: Susan E. Giuliani, ODEVI/DRMP, HFM-588

To: 125103/0 File

Subject: Filing Meeting Summary

Meeting Date: July 23, 2004 **Time:** 2:00 pm – 2:50 pm

Location: CDER WOC2 6FL-G Conf Room

Sponsor: Amgen, Incorporated

Product: Palifermin

Proposed Indication:

[redacted]

Purpose of meeting: To review the milestones, decide if the BLA can be filed, discuss remaining deficiencies, and to plan for future internal meetings.

Discussion:

The milestones were reviewed and the completed filing memos collected.

The Pharmacology/Toxicology reviewers found that the information included in the 5/14/04 first reviewable unit (RU) was complete for filing. The milestone "review for substantial completeness" was met (7/16/04). The CMA Pilot 1 does not require that a letter for this milestone be sent, however, the filing letter for the BLA will include a statement about the filing of this RU. The deadline for the discipline review letter is 11/16/04.

The product reviewer stated that raw data was not available in all aspects; however, due to the primary reviewer's knowledge of the IND and its supporting data, the tabular form of the raw data would most likely be sufficient. Additionally, any specific data that was

necessary could be requested on an as needed basis. An outstanding issue is the immunogenicity data. The product consultant stated that Amgen did not follow the guidelines and changed to a new immunogenicity detector in 2/04 after agreements with FDA were made and without first consulting with FDA. Amgen submitted additional information in integrated datasets initially on 7/2/04, per our request in a 6/10/04 telecon. Subsequently, Amgen informed the RPM that— samples were inadvertently left out from the 7/2/04 submission and Amgen had replaced the 7/1/04 submission with a new integrated dataset on 7/20/04. This information appeared to be available in CDER's electronic system, but must be reviewed for adequacy. The RPM was unsure at this point if the information was reviewable in the database provided by CDER, and would follow-up with OIT personnel. This also impacts the clinical review. (Follow-up: CDER OIT loaded the 7/20/04 document on 7/29/04 and the product consultant stated that he could adequately access the information. The aforementioned issues from the 6/10/04 telecon would be classified as review issues and comments will be generated for the Day 74 letter).

The clinical reviewer stated that all other clinical information was complete and reviewable and that this portion could be filed. A question that remains is Amgen's Quality of Life claims, but the issues are straightforward for possible discussion at ODAC. The clinical consultant was actively pursuing SGE's for ODAC and had a couple of possible candidates. The decision for going to ODAC was with the Division Director of DTBOP.

The facility reviewer stated that a recent inspection of the Boulder, CO facility for a [ ] from CDER's Office of Compliance. This action could halt production and licensing. A 483 was issued, and the OAI was at this time unconfirmed. Results from the Longmont facility inspection were pending and the facility reviewer would also check on the results from the [ ] facility inspection. The schedule for pre-inspection for this product is confirmed as the week of 9/27/04 to 10/1/04. The facility reviewer would route a copy of the 483 and EIR to the product reviewer. The RPM would schedule a post-inspection meeting, although this may not be needed. (Follow-up: An OAI was not issued and the pre-inspection dates are confirmed).

The clinical pharmacology reviewer stated the PK portion is straightforward and comparability issues are not apparent. This section could be filed. A question remains as to when Amgen would be submitting the renal deficiency study that was currently ongoing; during this review or during postmarketing? The RPM would request this information from Amgen.

The statistical reviewer stated that the statistical portion of the BLA was complete and could be filed.

The DSI reviewer stated that this information was complete. The clinical inspection sites were chosen and the inspection schedules would be completed within the next 2 – 3 weeks.

ODS had been consulted for the trade name review and for Amgen's risk management plans. DDMAC had been consulted for the promotional materials. The RPM would follow-up with the respective consultants.

The next internal meeting was the midcycle review on Friday, 9/10/04.

The meeting adjourned.

Decisions Reached:

- The filing of the BLA now depends on the adequacy of the immunogencity data submitted 7/20/04 by Amgen.
- The review team plans at this time to go to ODAC by actively seeking SGE's.
- Additional internal meetings will not be scheduled at this time.

Action Items:

- ☐ The product reviewer will follow-up with Amgen in regard to the possible need for additional raw data.
- ☐ The RPM will attempt to decipher Amgen's 7/20/04 electronic submission of immunogenicity data and if this information cannot be brought up in CDER's electronic system, the RPM will contact OIT personnel. (Follow-up 7/29/04: This issue was resolved).
- ☐ Once the 7/20/04 immunogenicity submission is loaded and reviewable, the reviewers will confirm that the data is integrated and adequately complete for filing by the action deadline of Friday, 8/13/04.
- ☐ The DTBOP Division Director will follow-up with the review team regarding the need for participation in ODAC and dates.
- ☐ The facility reviewer will follow-up with the review team regarding results of inspections, the possible OAI, and will route a copy of the EIR and 483 to the product reviewer.
- ☐ The RPM will propose an October 2004 date for a post-inspection internal meeting, although this may not be needed.
- ☐ The RPM will follow-up with Amgen regarding submission of the results of the ongoing renal deficiency study.

- The RPM will follow-up with ODS and DDMAC consultants regarding review of the proposed trade name, the proposed risk management plan, and the promotional materials.

FDA Attendees: Patricia Dinndorf, Mark Rothmann, Hong Zhao, Anita O'Connor, Ralph Bernstein, Javier Tavarez-Pagen, Marlene Swider, John V. Kelsey, Earl Dye, Susan Giuliani

DAY 74 Letter ...August 27, 2004 Meeting

Our STN: BL 125103/0
Amgen, Incorporated
Attention: Ross Lobell
Director, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. Lobell:

Please refer to your biologics license application (BLA) for Palifermin, submitted under

section

351 of the Public Health Service Act, and to our filing letter dated August 13, 2004.

While conducting our filing review we identified the following potential review issues:

PRODUCT INFORMATION:

1. As communicated in the teleconference held June 10, 2004, between representatives of Amgen and representatives of FDA, the FDA regards the terms "cutpoint" and "threshold" as identical. The cutpoint is a value below which patient samples are considered negative for the presence of antibodies and above which samples are considered positive. A determination of positive response may then lead to further analysis (e.g., immunodepletion). This value should be determined by the analysis of normal or preferably, pre-dose patient samples. A statistical analysis of these values should be performed to define the cutpoint and handling of outlier values should be addressed. An [ ] for the cutpoint is recommended to ensure that the definition of positivity is sufficiently sensitive to pick up all potential immune responses, i.e., it is more appropriate to have [ ], than false negatives.

Despite the Agency's previous advice on cutpoint determination, we note that you have not employed this approach in the determination of cutpoint for the anti-Palifermin immunogenicity assay. Since this determination is critical to the determination of immunogenicity rates and testing for neutralizing antibodies, this deficiency may impact the ability to adequately label the product, should the product be approved.

Please address the above concern regarding cutpoint definition and its application to the interpretation of clinical trial immunogenicity data.

FACILITY INFORMATION:

2. As discussed during the August 25, 2004, telephone conversation between Dr. Geaza Ekecs of Amgen, Incorporated (LakeCentre Facility, Boulder, CO) and Ms. Marlene Swider of FDA, please provide a reference list of current standard operating procedures (SOPs) describing the activities in the manufacture of Palifermin.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application. Following a review of the application, we shall advise you in writing of any action we have taken and request additional information if needed.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cder/biologics/default.htm. Until further notice, however, all correspondence should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

If you have any questions, please contact the Regulatory Project Manager, Susan Giuliani, at (301) 827-5101.

Sincerely,

Susan E. Giuliani, R.N., M.S.
Regulatory Project Manager
Division of Review Management and Policy
Office of Drug Evaluation VI, CDER

MID-CYCLE MEETING, September 10, 2004:

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

From: Susan E. Giuliani, ODEVI/DRMP, HFM-588

To: STN 125103/0 File

Subject: Midcycle Meeting Summary

Meeting Date: September 10, 2004 **Time:** 1:00 pm – 4:00 pm

Location: CDER WOC II, 6th Floor Conference Room G

Sponsor: Amgen, Incorporated

Product: Palifermin

Proposed Indication:
[ ]

Type of meeting: Midcycle Review

Meeting Purpose: To obtain the status of the reviews and to plan towards label negotiations and final action.

Introduction:

The agenda, background, and milestones were reviewed. The final reviews are to be completed by November 24, 2004 so that tertiary reviews and signatures can be accomplished.

Review Status:

1. DDMAC: Ms. Broadnax identified language in Amgen's proposed package insert label that is promotional and that should be modified and/or support by substantial evidence. Labeling recommendations will be discussed in more detail in the upcoming labeling meetings.

2. PRODUCT: Dr. Stromberg noted that the product is adequately characterized, and that consistency of manufacture is indicated by nearly identical impurity profiles in the clinical and conformance DS and DP lots. However, prior to the submission of the BLA, Amgen was asked to perform [ ] studies. This data, not yet received, is expected prior to the planned inspection planned for September 26- October 1, 2004 and will clarify the specification for product [ ] Amgen will also analyze additional conformance lots of drug product manufactured at — to validate the manufacturing process [ ] The stability data for the DS and DP are still under review but would appear to support Amgen's proposed expiration dating period of [ ] for the DS and 18 months for the DP at the recommended storage conditions ([ ] for DS and refrigerated for DP)

3. PRODUCT CONSULTANT: Dr. Bernstein noted that Amgen has not yet satisfactorily addressed the Agency's concern regarding the cutpoint in the immunogenicity assay used to determine positivity. If the cutpoint is lowered, Amgen may need to do more testing. This issue will be discussed in a telecon requested by Amgen and scheduled to occur on 9/22/04.

4. FACILITY: Ms. Swider reported that Amgen received a form 483 for its Lake Centre facility. [ ] The inspection is currently scheduled for 9/27/04 through October 4, 2004. The drug substance review is almost complete and additional information will be requested with regard to updated SOPs, floorplans and lot number coding .

5. SCIENTIFIC INVESTIGATIONS (DSI): Jose Tavarez-Pagan reported that two clinical sites were chosen for inspections due to high enrollment and high efficacy rates. An inspection at one site has been completed and appears acceptable with the exception of minor protocol deviations. The second inspection is near completion.

6. PHARMACOLOGY/TOXICOLOGY: Dr. Wilcox noted that the review is in process. Toxicities identified to date are those expected based on pharmacological activity. NOAEL not determined; activity seen at the lowest doses. Amgen has requested pregnancy category C. The product seems to have some effect on the survival of embryos in animal models. The review team discussed the potential for tumor promotion. Consensus was reached that the label will need to reflect the lack of data with respect to tumor promotion potential. This issue was deferred until submission of the solid tumor indications. However, this issue must be dealt with appropriately in this label.

7. CLINICAL PHARMACOLOGY: Dr. Zhao reviewed data from 8 PK studies. The review thus far has identified no major problems. The incidence of adverse events increased with dose. Bioequivalence studies were not conducted by Amgen because changes were not expected to affect safety or efficacy. The renal impairment study is ongoing. Amgen apparently did not conduct interaction studies but there are no concerns regarding the product's effect on other drugs.

8. CLINICAL/STATISTICAL and CONSULTANTS: Dr. Dinndorf noted that the WHO scale was used in the pivotal study for the primary endpoint. The reviews are ongoing and the statistical consultant, Dr. Kammerman, is reviewing the consistency of the quality of life (QOL) scales used in the efficacy evaluation. The safety review to date indicates that a skin rash may have unblinded the results. Special attention will be given to assessment of Amgen's proposed wording in the label regarding non-pre-specified secondary endpoints (incidence of fever and neutropenia, mean mg morphine required and the incidence of the requirement for TPN).

Advisory Committee:

Clinical is the only review that may have issues for discussion at the oncology drugs advisory committee (ODAC), and these issues could be dealt with as individual questions to the respective AC experts. At this time, the decision of the team is in favor of not going to the Advisory Committee, but this decision could change depending on the ongoing reviews. The RPM will follow up with the DTBOP Division Director with regard to the final deadline for ODAC.

Pediatric Deferral:

After discussions with the Children's Oncology Group, Amgen is amending the proposed protocol submitted to the IND on 5/28/04. Amgen requested a deferral in the cover letter of the 6/15/04 BLA submission, and the study timelines will need to change. FDA will notify Amgen of the appropriate strategy for dealing with this change at the informal 9/22/04 telecon requested by Amgen.

Postmarketing Commitments:

The following are under consideration as PMC studies:

- Renal PK
- Tumor proliferation in animal models with solid tumors
- First dose and/or multiple dosing
- Long term follow-up
- Second cancer
- Reaction with GVHD
- Allogeneic population
- **Major Labeling Issues/Discrepances:**

ODS/DDRE has reviewed Amgen's risk management plan (RMP) and stated it was acceptable from a theoretical standpoint. The RPM will provide to the DTBOP division director a listing of the specific study(ies) Amgen proposes to conduct for the RMP. In addition, the RPM will follow up with those ODS staff consultants who are reviewing Amgen's proposed proprietary name for Palifermin. Two labeling meetings are scheduled in November.

Additional Item:

➢ The clinical review of Amgen's financial disclosure information is complete and is acceptable.

Decisions Reached:

✓ The main issues that must be addressed by Amgen before the action deadline are product purity [ ] immunogenicity, and OAI.

✓ Currently, the plan is not to present this product at the ODAC meeting.

Action Items:

The deficiencies with respect to immunogenicity and appropriate regulatory strategy for the Pediatric deferral will be discussed in a telecon on 9/22/04.

The facility reviewer will send copies of the 483 to the team members and keep the team members updated on the OAI.

The RPM will follow up with the DTBOP Division Director with regard to the final deadline for ODAC.

The RPM will follow up with ODS reviewers assigned to the review of Amgen's proposed propriety name.

The RPM will provide to the DTBOP division director the specific proposed study(ies) Amgen proposes to conduct for the RMP.

The RPM will schedule a follow-up committee meeting in Mid-October, 2004.

Participants:

Karen Weiss, David B. Ross, Glen D. Jones, Patricia Keegan,
Robert Justice, Joseph Gootenberg, Patricia Dinndorf, Kaushikumar Shastri,
Fred Hyman, Mark Rothmann, Lisa Kammerman, Hong Zhao, Barbara Wilcox,
Kurt Stromberg, Emily Shacter, Carole Broadnax, Jose J. Tavarez, Marlene G. Swider,
Jianming Li, Carole Broadnax, Earl Dye, Karen Jones, Susan Giuliani

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

From: Susan Giuliani, ODEVI/DRMP, HFM-589

To: The 125103/0 file

Subject: Teleconference Summary

Teleconference Date: September 22, 2004 **Time:** 3:00 pm – 3:30 pm

Location: CDER WOC2 6th Floor, Conference Room H

Sponsor: Amgen, Incorporated

Product: Palifermin

Proposed Use:

Purpose of call: To reach agreement on the contents of the upcoming 120-day safety update, to clarify outstanding items related to revising the Pediatric protocol, and to clarify the status of the review of the proposed proprietary name and immunogenicity.

Background:

Amgen sent a fax of questions on 9/1/04 with a request for this non-PDUFA telecon. FDA faxed responses to Amgen's questions on 9/20/04 and added a question re: location of immunogenicity information in the BLA. Amgen responded to the latter in a fax transmitted 9/21/04. These faxes are attached at the end of this summary. The discussion and agreements are outlined below:

Discussion Points:

1. The FDA and Amgen discussed and agreed to the following items with respect to the upcoming 120-day safety update:

   - The final study report for study 20030142 (renal impairment) will not be included in the 120 day safety update.

- Safety data from study 20020182 Part B (data for 8 patients) will be included.
- 0020162, 20020182 Part A and 2030142 were included in the original BLA submission. Amgen will provide an integrated report of all additional slit lamp testing, including the data currently in the application under the individual studies and additional data from study 20020182 Part B in the 120 day safety update. Amgen noted that the data has been reviewed by an independent ophthalmologist, whose assessment in part of the integrated report. Amgen clarified that the slit lamp testing data from Studies 20020161, 20010182 Part A and 20030142 were included in the original BLA submission. FDA agrees that Amgen may submit this data because it does not constitute a substantial amount of new data.

2. Regarding Amgen's request for deferral of pediatric studies included in the 6/15/04 cover letter of the BLA, Amgen agreed to submit a revised proposal as soon as possible that will include the following:

   - Description of the pediatric studies to be conducted under PREA for which deferral is requested.
   - All milestones
   - Age groups to be studied A reference to the original deferral request contained in the cover letter of the 6/15/04 BLA submission.

3. Regarding immunogenicity information included in the BLA, the following was discussed and clarified:

   - The table on page 3 of Amgen's 9/21/04 fax identifies patient's ID number and the study protocol number who are reactive in assays for immunogenicity, according to the modified cut-point.

   In the July, 2004 submission Amgen presented data according to a modified immunogenicity assay cutpoint (1.21) rather than the cut-point of from — in the original immunogenicity assay. Samples were considered to be reactive if the signal to noise (S/N) ratio was — . If the S/N ratio was ≥ 1.21 but less than — the samples were considered to be positive below the quantitation limit. If the S/N ratio was — the samples were immunodepleted using — ng/mL unlabeled Palifermin as a competitor and then re-analyzed. Samples showing a — reduction in S/N ratio were considered confirmed positives. In response to an FDA question, Amgen stated that the rationale for using 800ng/mL of competitor as opposed to — ng/mL originally used was to ensure that high levels of antibody could be fully competed.

   Amgen was informed that the immunogenicity information is still under review and the FDA reviewer may call Amgen for any additional clarifications and/or information.

4. Regarding the proposed proprietary name for Palifermin (still under review) Amgen informed FDA that neither of the two proposed trade names were deemed acceptable in Europe due to concerns about the potential for medication errors arising from drug products with similar names. Amgen will submit a revised proposal with a request for expedited review early next week.

Additional Item:

- FDA requested that Amgen submit proposals for all postmarketing commitments (PMCs) that include all required milestones as soon as possible. The PMCs should include the renal impairment study, the long-term safety study, and the preclinical tumorigenicity study, as well as the pediatric study previously discussed. Amgen agreed to do so.

Action Items:

Amgen will submit the following information to the BLA:

- ✓ All agreed-upon items in the 120-day update
- ✓ A revised proposal for deferral of pediatric studies
- ✓ A new proposed proprietary name for FDA review
- ✓ Proposals for PMCs

FDA RPM will follow-up with the FDA reviewer regarding the immunogenicity information.

FDA Attendees: Patricia Keegan, Joseph Gootenberg, Patricia Dinndorf, Karen Jones, Susan Giuliani

Amgen Attendees: Julie Lepin, Tom Tarlow, Mon-Gy Chen, Kerr Clark, Jamie Finn, Urte Gayko, Shalini Gupta, Gene Koren, David Parkinson, Linda Paradiso, Kathy Jelaka-Maxwell, Alessandra Cesano.

Information Requests/Telecon (not usually formal)
Review #1
Deficiency communication[3]
Amendment
T-con
Discipline review letter

[1] Chronology of previous CMC communications between CDER and the firm and/or reviews

[2] Applicant's letter date or date of review and/or communication with applicant

[3] For OBP – IR letter or action letter

483 Observations from Sept 28th to October 2 Inspection of Palifermin Manuf. Facility:

17 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

The Biochemistry Executive Summary

Brief summary of Quality of Palifermin Drug Substance and Drug Product

Palifermin is ultimately derived from chemical synthesis of the nucleotide gene sequence specifying the amino acid sequence of native human Keratinocyte Growth Factor-1 (also known as Fibroblast Growth Factor 7), with the exception that the N-terminal 24 amino acids are deleted from the recombinant protein. The

The working cell bank is successively expanded to then to commercial scale of which yields approximately Palifermin Drug Substance. Purification is achieved process.

The final product is at least pure human recombinant KGF. The minor impurities are comprised of that are approximately

The following characterization data summarizes the product-related variants of the DS: 1) analysis of Palifermin indicates representing approximately of the total integrated area/ This was identified as a palifermin

2) Analysis by , that was identified as palifermin variant. was tentatively identified as a palifermin variant containing These are present at a level of total integrated area. 3) Finally, indicate about of DS product is in . Analysis of Western Blots

] but was less quantitative. tests included [ ] Thus, in a cumulative determination, approximately — of the Palifermin protein represents either [ ] variants derived from Palifermin production. Process-related impurities were low [ ] adequate acceptance criteria. [ ] E. coli cell protein was less that [ ]

]Adequate Palifermin DS Release and Stability Specifications assure the quality, consistency and stability of the Palifermin DS.

A [ ] bioassay measures mitogensis induced by Palifermin DS and DP. This validated potency assay has an intra-assay and inter-assay coefficient of variation of [ ] respectively, and is based on comparison to the activity of a Palifermin Reference Standard. The bioactivity of the reference standard in this assay will be controlled to prevent drift in product activity over the years ahead.

The commercial scale product (approximately [ ] is shown by extensive chemical and physical characterization to be comparable to the clinical lots used to establish efficacy and safety of Palifermin.

The Palifermin drug product is formulated by [ ] Storage is a 2-8 C. Each product vial contains 6.25 mg of lyophilized Palifermin DP and is reconstitutes in 1.2 mL of Sterile WFI to yield a 5.0 mg/mL concentration for IV bolus injection.

Moreover, stability-indicating tests establish that the DS and DP lots are stable at the proposed expiries of [ ] and 18 months for refrigerated DP

1. To discuss any unique scientific and regulatory issues that had a significant effect on the review decision

Specifications

Discuss removal ot[ ]as DS and DP specifications [ ] DP release specification.

[ ]

Evaluation of—DS conformance lots [ ] showed [ ] in non-reduced conditions with [ ]These used an assay method of [ ] is more sensitive for — detection than the[ ] shown in DP analysis in P.2.3.6.

Photostability of lyophilized and reconstituted Drug Product.

Both Palifermin lyophilized DP and reconstituted DP [ ]. However, this exceeds by about [ ] the light exposure that occurs under expected clinical conditions in a hospital [ ]. The Palifermin Package Insert has been revised to adequately emphasize the requirement to protect the product from light exposure. In addition, a PMC requires a light exposure and stability study of Palifermin under clinical conditions of use at the bedside.

[ ] Testing

[ ] as a Drug Substance Release Test or use of [ ] after the DS [ ] with a [ ] of greater than [ ] is an issue that remains under discussion among DTP, TFRB and Compliance.

2. To describe the attributes of the drug product that can affect safety.
   Palifermin drug product degrades after hours of intense light exposure of either lyophilized or reconstituted drug product. This photosensitivity is adequately managed by following the Package Insert's "Instruction for Use" of Palifermin.
   The Palifermin drug product does not appear to present a safety concern in respect to immunogenicity, given the very low detection in clinical trials and the high redundancy within the very large FGF family of grow factors.

3. To very briefly describe the deficiencies found in the application.
   Discussions with Amgen led to tightening the Release and Stability Specifications for both the drug substance and drug product to the extent that this is no longer a deficiency. This occurred despite only having only a small commercial manufacturing data base of – lots. Amgen estimates that [ ] will not be needed again [ ]. During the product review cycle several test methods, particularly [ ] for immunogenicity detection and assay for neutralization, were made more sensitive and reliable. [ ] In-process Control tests were added where needed. In summary, no significant deficiencies were identified in this BLA.

4. To discuss risk management steps (e.g., tighter specifications or stability requirements for the drug substance and/or drug product).
   See # 5 above

5. To provide reasons for accepting post-approval commitments or agreements.
   The PMCs listed in the Executive Summary above are used to assure improvement in product manufacturing in the future and to respond to the present CMC concerns.

6. To provide the reviewers recommendation on approval, non-approval, or approvability from a biochemistry perspective.

Approval of the Palifermin BLA is based on the submission of fully adequate Biochemistry, Manufacturing and Control documentation for this recombinant form of human Keratinocyte Growth Factor. This includes thorough information and data on manufacturing controls, methods and process validation, product characterization (purity and product and non-product related impurities), consistency of manufacture (comparability of pilot, clinical and commercial lots of Palifermin), specifications, and stability data.

Palifermin is a highly purified and well-characterized product with release specifications that will ensure lot-to-lot consistency. The manufacturing process is under control and has been satisfactorily validated. The clinical and conformance lots of drug substance and drug product were comparable. The product has a high degree of stability in the liquid form, and the low extent of instability of the lyophilized and reconstituted drug product has been carefully examined. and will remain within specifications if stored as recommended during the assigned shelf life of 30 month for drug substance and 18 months for lyophilized drug product.

Immunogenicity does not appear to be a concern for this product. Patients receiving repeated Palifermin treatment showed a low incidence — of antibody detection without development of neutralizing antibodies. KGF is protein within the 22-member FGF family of growth factor; consequently, with this high redundancy, patients developing antibodies would not be expected to experience long term or severe side effects.

I. Recommendations

The Division of Therapeutic Proteins, OBP, OPS, CDER recommends approval of BLA #125103, and the Post-Marketing Commitments as discussed below.

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Palifermin is the USAN name for Amgen's Keratinocyte Growth Factor-1 (KGF-1), a member of the Fibroblast Growth Factor Family within which KGF-1 is also known as FGF-7. Palifermin is manufactured via recombinant DNA technology in *E. coli*, [ ] drug substance (DS) that begins at the N-terminal amino acid #24 of native Human KGF. The Palifermin Drug Substance is [ ] lyophilized drug product (DP) for refrigerated storage.

Palifermin is an N-terminal 23 amino acid truncation of native human Keratinocyte Growth Factor that was discovered by Rubin et al and published in PNAS in 1989. KGF is a paracrine protein growth factor produced by mesenchymal cells, particularly sub-epithelial fibroblasts, and binds FGFR-4, which is a splice variant of FGFR IIIb expressed in many epithelial cells. After binding FGFR-4, KGF initiates epithelial cell

proliferation, migration and up-regulates expression of numerous protective cell functions. As listed in the Palifermin Package Insert, native human KGF has trophic effects on many types of epithelial surfaces and tissues including tongue, buccal mucosa, esophagus, stomach, intestine, salivary gland, lung, liver, pancreas, kidney, bladder, mammary gland, and skin (hair follicles and sebaceous gland, and the lens of the eye. The KGF receptor is not present in cells of the hematopoietic lineage.

B. Description of How the Drug Product is Intended to be Used

At the bedside, Palifermin DP is reconstituted in WFI for IV bolus injection as an adjunctive treatment of adult hematological malignancies to mitigate mucositis attendant to myeloablative therapy with radiation and chemotherapy.

C. Basis for Approvability or Not-Approval Recommendation

Approvability is based on the submission of fully adequate Biochemistry, Manufacturing and Control documentation for this recombinant form of human Keratinocyte Growth Factor. This includes thorough information and data on manufacturing controls, methods and process validation, product characterization (purity and product and non-product related impurities), consistency of manufacture (comparability of pilot, clinical and commercial lots of Palifermin), specifications, and stability data.

Palifermin is a highly purified and well-characterized product with release specifications that will ensure lot-to-lot consistency. The manufacturing process is under control and has been satisfactorily validated. The clinical and conformance lots of drug substance and drug product were comparable. The product has a high degree of stability in the liquid form, and the low extent instability of the lyophilized and reconstituted drug product has been carefully examined., and will remain within specifications if stored as recommended during the assigned shelf life of [ ] for drug substance and 18 months for lyophilized drug product.

Immunogenicity does not appear to be a concern for this product. Patients receiving repeated Palifermin treatment showed a low incidence [ ] of antibody detection without development of neutralizing antibodies. KGF is protein within the 22-member FGF family of growth factor; consequently, with this high redundancy, patients developing antibodies would not be expected to experience long term or severe side effects.

II. Administrative

A. Reviewer's Signatures Kurt Stromberg, M.D 12/14/04
Ralph Bernstein, PhD
Supervisor Emily Shacter, PhD

B. Endorsement Block

173 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling