CUBIST
PHARMACEUTICALS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.:	4,885,243
Issued:	December 5, 1989
Inventors:	Floyd M. Huber et al.
Assignee:	Cubist Pharmaceuticals Inc.
Application No.:	06/773,762
Filed:	September 9, 1985
For:	PROCESS FOR PRODUCING A-21978C DERIVATIVES

Mail Stop Patent Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM PURSUANT TO 35 U.S.C. §156

Cubist Pharmaceuticals Inc., a corporation organized and existing under the laws of the state of Delaware (hereafter "Applicant" or "Cubist"), represents that it is the owner of the entire interest in and to U.S. Patent No. 4,885,243 ("the '243 patent") by virtue of an assignment in favor of Applicant recorded on September 25, 2003, at Reel 013998, Frame 0710. A copy of the applicable Notice of Recordation of Assignment is attached as Exhibit A to this Application. Pursuant to 35 U.S.C. § 156, Applicant, acting through its duly authorized, registered attorney, hereby submits this Application for Extension of Patent Term (hereafter "Application") for the above-identified patent by providing the following information required by 37 C.F.R. § 1.740.

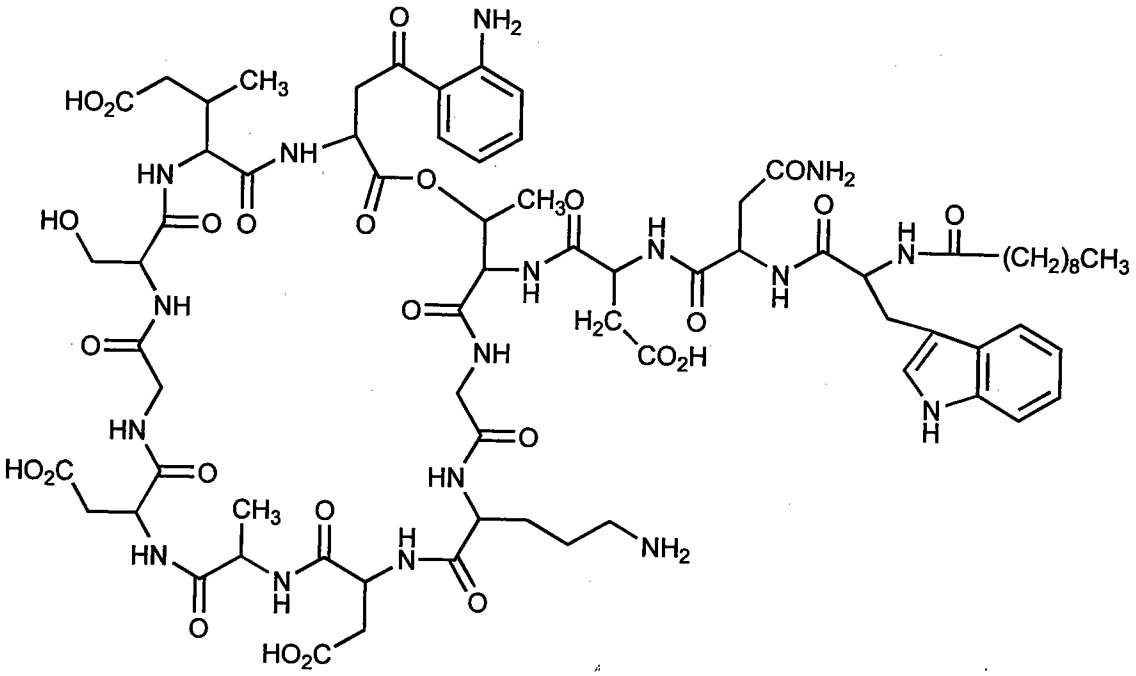
Identification of the Approved Product

Trade Name: CUBICIN

Generic name: Daptomycin

Chemical Name: *N*-decanoyl-L-tryptophyl-L-asparaginyl-L-aspartyl-L-threonylglycl-L-ornithyl-L-aspartyl-D-alanyl-L-aspartylglycyl-D-seryl-*threo*-3-methyl-L-glutamyl-3-anthraniloyl-L-alanine ε_1-lactone.

The chemical structure of daptomycin is:



Identification of the Federal Statute under which Regulatory Review Occurred

The approved product, CUBICIN™ (daptomycin for injection), was reviewed under the Federal Food, Drug, and Cosmetic Act, Section 505 (21 U.S.C. § 355).

Date on which the Product Received Permission for Commercial Marketing or Use

The approved product, CUBICIN™ (daptomycin for injection), was approved for commercial marketing or use under Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355) on September 12, 2003.

Active Ingredient has not been Previously Approved for Commercial Marketing or Use

The only active ingredient in CUBICIN™ is daptomycin, which has not been approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act prior to the approval of NDA 21-572 by the Food and Drug Administration ("FDA") on September 12, 2003.

Timely Submission of this Application

This Application is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. § 1.720(f). The last day for submission of the application is November 11, 2003. Accordingly, the Application is timely submitted.

Identification of the Patent for which an Extension is being Sought

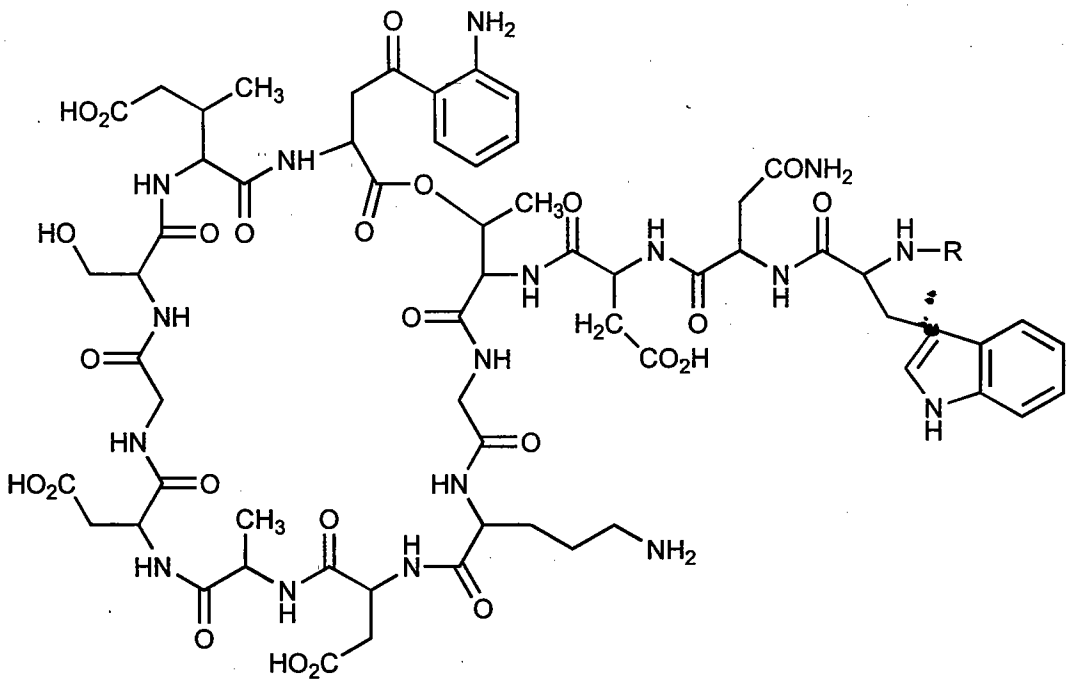
A patent term extension is being sought for the '243 patent. The inventors are Floyd M. Huber, Richard L. Pieper and Anthony J. Tietz. The '243 patent issued on December 5, 1989 and it is currently due to expire on December 5, 2006.

Pursuant to 37 C.F.R. § 1.740 (a)(7), a copy of the '243 patent is attached as Exhibit B to this Application. Pursuant to 37 C.F.R. § 1.740 (a)(8), receipts of maintenance fee payments made for the '243 patent are attached as Exhibit C to this Application.

The '243 Patent Covers a Method of Manufacturing the Approved Product

The '243 patent claims a method of manufacturing the approved product, CUBICIN™ (daptomycin for injection). In particular, claims 1, 2 and 7 of the '243 patent claim a process that encompasses the method of manufacturing daptomycin.

Claim 1 of the '243 patent claims a process for producing an A-21978C derivative of the formula:



wherein R is a C_2-C_{14}-alkanoyl group. When R is a C_{10}-alkanoyl group, namely, n-decanoyl (-C(O)(CH2)$_8$CH$_3$)), the compound of the formula in claim 1 is daptomycin, the approved product.

Claim 1 of the '243 Patent	NDA 21-572
In the process for producing an A-21978C derivative of the formula [see above] wherein R is a C_2-C_{14}-alkanoyl group	The approved product (daptomycin) is an A-21978C derivative of the formula in claim 1 when R is a C_{10}-alkanoyl group, namely, n-decanoyl (-C(O)(CH2)$_8$CH$_3$)).
the improvement which comprises feeding the corresponding ROH acid, or an ester or a salt thereof,	The corresponding ROH acid of n-decanoyl is decanoic acid, which is fed during the fermentation process. *See* page 83, Fig. 4.4: Process Flow Diagram – Fermentation; page 86, Table 4-30: Critical Process Flow Parameters – Main Fermentation.
to an A-21978C-producing *Streptomyces roseosporus* culture selected from NRRL 11379, NRRL 15998, or an A-21978C-producing mutant thereof	The commercial production strain used in the method of manufacturing the approved product is NRRL 15998. *See* page 44, section 4.1.1., Chemistry, Manufacturing and Control data section.
during the production stage of the fermentation until the A-21978C derivative is produced.	The *S. roseosporus* is grown in the presence of decanoic acid to produce daptomycin. *See* page 85, section 4.3.2.1.; Table 4-31: Process Measurables – Main Fermentation

Claim 1 recites the process of producing an A-21978C derivative (daptomycin) by feeding the corresponding ROH acid (decanoic (or capric) acid) to an A-21978C producing strain (NRRL 15998) during the production stage of the fermentation until daptomycin is produced. Thus, as shown in the table above, claim 1 corresponds to the method of manufacturing the active ingredient of the approved product, daptomycin.

Claim 2 recites the process of claim 1, wherein a C_2-C_{14}-alkanoic acid is used. Decanoic acid, which is used in the method of manufacturing the active ingredient of the approved product is a C_{10}-alkanoic acid, and thus claim 2 also corresponds to the method of manufacturing daptomycin.

Claim 7 recites the process of claim 2, wherein capric acid is used. The term "capric" is the common name for "decanoic" and is used interchangeably with the term "decanoic" in the '243 patent. *See* col. 6, line 15. Thus, claim 7 also corresponds to the method of manufacturing the approved product.

Statement Pursuant to 37 C.F.R. § 1.740 (a)(10)

Pursuant to 35 U.S.C. § 156(g), the relevant dates and information to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(i) Investigational New Drug Application No 27,627 ("IND 27,627") was filed by Eli Lilly and Company ('Lilly") on December 20, 1985 and became effective on January 18, 1986.

(ii) Investigational New Drug Application No. 57,693 ("IND 57,693") was filed by Applicant on December 31, 1998 and became effective on January 29, 1999.

(iii) New Drug Application No.21-572 ("NDA 21-572") was filed by Applicant on December 20, 2002 and approved on September 12, 2003.

Statement Pursuant to 37 C.F.R. § 1.740 (a)(11)

Attached as Exhibit D is a chronology of the major communication between Lilly and the FDA concerning IND 27,627 and attached as Exhibit E is a chronology of the major communication between Applicant and FDA concerning IND 57,693 and NDA 21-572. In addition, Applicant submits the following brief description of the activities during the applicable regulatory review period.

Daptomycin was discovered by scientists at Lilly and was selected for development in 1984 as an intravenous drug to treat serious gram-positive infections including endocarditis and skin and skin structure infections. Lilly filed IND 27,627 on December 20, 1985. Most of the preclinical safety, Phase I and Phase II clinical studies were conducted in the United States under IND 27,627. The compound was evaluated in nineteen Phase I and two Phase II studies. Seven Phase I studies were conducted in Japan, Spain and Italy; and selected investigators in Canada, Spain and the United Kingdom participated in these clinical research protocols. France participated in the Phase II trials under a Clinical Trial Exemption submitted June 1, 1988.

In June 1987, a Phase II clinical trial (B8B-MC-AVAE/B8B-EW-AVAG) was initiated by Lilly to evaluate the efficacy of daptomycin at a dose of 2mg/kg administered every 24 hours. This dose regimen appeared to be effective in skin and skin structure infections, but not against bacteremia and deep-seated infections. A second Phase II trial (B8B-MC-AVAM), initiated in June, 1989 demonstrated that daptomycin at 3mg/kg administered every 12 hours over a 14 day period was potentially effective in bacteremia, but was less effective than conventional therapy for staphylococcal endocarditis. A further Phase I study evaluated the safety of 4mg/kg administered over 12 hour over a 14 day period. This study was discontinued when 2 of 5 subjects experienced muscle-related adverse events (forearm weakness, myalgia, and elevated creatinine phosphokinase (CPK)).

Based upon the questionable efficacy in the treatment of endocarditis and transient skeletal muscle toxicity at the highest dose evaluated in the treatment of endocarditis, 5mg/kg administered every 12 hours, Lilly voluntarily suspended worldwide clinical investigations and so informed the Division of Anti-Infective Drug Products, FDA, on March 8, 1991. On April 3, 1991 the Division placed daptomycin on

formal clinical hold. Clinical studies under IND 27,627 were not resumed and the IND was placed on inactive status in January 1992 at the sponsor's formal request submitted to FDA on December 17, 1991.

Between 1991 and 1997, the need for additional therapies for Gram-positive infections had grown dramatically, as evidenced by increased incidence of serious, life-threatening infections, including bacteremia, and the emergence of progressive antimicrobial resistance, particularly among isolates of *Staphlococcal aureus, Staphlococcal pneumoniae,* and enterococci.

In recognition of the public health need, Applicant licensed worldwide rights to daptomycin from Lilly in November 1997 and submitted a new IND to FDA for continuation of clinical development of daptomycin on December 31, 1998. Applicant's IND became effective on January 29, 1999 and was opened by FDA under IND No. 57, 693.

Between 1997 and 1998, Applicant engaged in a series of communications with FDA to define the daptomycin clinical development plan. The overall result yielded the submission of NDA 21-572 on December 20, 2002.

At a joint FDA-Cubist meeting in July 1998, FDA expressed no reservations about the Phase III development plan for the indication of complicated skin and skin structure infections. However, FDA wished to reassess bacteremia as a primary indication. In November 1998, Applicant proposed conducting two pivotal Phase III trials of daptomycin in the complicated skin and skin structure infection (cSSSI) indication, Protocol DAP-SST-9801 in the US and Protocol DAP-SST-9901 in Europe and South Africa. The two protocols were identical other than the comparator agents used to mimic actual medical practice unique to each geographic region. The comparator agents themselves were generally equivalent in therapeutic efficacy. The rationale for investigating daptomycin in the treatment of cSSSI originated in the fact that daptomycin is rapidly bactericidal against Gram-positive pathogens commonly associated with this clinical syndrome; supported by the pre-clinical and earlier Phase II clinical trial conducted under IND 27,627.

By May 2001, Protocol DAP-SST–9901 had completed enrollment. Protocol DAP-SST-9801 continued to progress slowly due to enrollment difficulties.

A joint Cubist-FDA meeting was held March 4, 2002 where FDA agreed with Applicant that an NDA for daptomycin could be filed in CSSSI based on the above two mentioned studies. In further discussions with FDA in October 2002, it was agreed that Applicant would submit the integrated clinical and statistical reports containing all safety and primary efficacy data for all ongoing clinical research within the NDA application. All additional analyses along with microbiological and nonclinical data pertaining to the efficacy of daptomycin in other indications, would be submitted as an amendment to IND 57,693. This amendment was filed within 30 days after submission of the NDA for cSSSI.

Eligibility and Calculation of Patent Term Extension Pursuant to 37 C.F.R. § 1.740 (a)(12)

Applicant is of the opinion that U.S. Patent No. 4,885,243 is eligible for extension under 35 U.S.C. 156 because it satisfies all of the requirements for such extension as follows:

(a) The '243 patent claims a method of manufacturing the approved product, CUBICIN™ (daptomycin for injection). 35 U.S.C. § 156(a).

(b) The term of the '243 patent has not expired before submission of this application. 35 U.S.C. § 156(a)(1).

(c) The term of the '243 patent has never been extended. 35 U.S.C. § 156(a)(2).

(d) The application for extension is submitted by the owner of record in accordance with the requirement of 35 U.S.C. § 156(d) and rules of the U.S. Patent and Trademark Office. 35 U.S.C. § 156(a)(3).

(e) The product, CUBICIN™ (daptomycin for injection), has been subjected to a regulatory review period before its commercial marketing or use. 35 U.S.C. § 156(a)(4).

(f) The commercial marketing or use of the product, CUBICIN™ (daptomycin for injection), after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) under which such regulatory review period occurred. 35 U.S.C. § 156(a)(5)(A).

(g) No other patent has been extended for the same regulatory review period for the approved product, CUBICIN™ (daptomycin for injection). 35 U.S.C. § 156(c)(4).

The length of extension of the patent term of the '243 patent claimed by Applicant is 1,347 days or 3.69 years. The length of extension was determined pursuant to 37 C.F.R § 1.775 as follows:

(a) The regulatory review period under 35 U.S.C. § 156(g)(1)(B) is a total of 3,845 days or 10.53 years, which is the sum of the Testing Period under IND 27,627, the Testing Period for IND 57,693, and the Application Period for NDA 21-572. These periods of review were calculated as follows:

(1) The period of review under 35 U.S.C. § 156(g)(1)(B)(i) for IND 27,627, the "Testing Period for IND 27,627," began on January 18, 1986 and ended on December 17, 1991, which is 2,159 or 5.92 years.

(2) The period of review under 35 U.S.C. § 156(g)(1)(B)(i) for IND 57,693. the "Testing Period for IND 57,693," began on January 29, 1999 and ended on December 19, 2002, which is 1,420 days or 3.89 years.

(3) The period of review under 35 U.S.C. § 156(g)(1)(B)(ii) for NDA 21-572, the "Application Period" began on December 20, 2002 and ended on September 12, 2003, which is 266 days or 0.73 years.

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined above (3,845 days), less:

(1) The number of days which were on or before the day on which the patent issued (January 18, 1986 to December 5, 1989) which is 1,417 days; and

(2) The number of days during which the Applicant did not act with due diligence, which is zero (0) days; and

(3) One-half the sum of the number of days determined in sub-paragraphs (a)(1) and (a)(2) after the patent issued [(2,159 + 1,420 – 1,417)/2] or 1,081 days;

(4) The regulatory period is calculated by subtracting the number of days determined in sub-paragraphs (b)(1) through (b)(3) from the entire regulatory review period as determined above (3,845 days - 1,417 days – 0 days - 1,081 days) which equals 1,347 days.

(c) The number of days as determined in sub-paragraph (b)(4) (1,347 days) when added to the original term of the patent (December 5, 2006, as determined by 35 U.S.C. § 154(c)) would result in the date August 13, 2010.

(d) Fourteen (14) years when added to the date of NDA approval (September 12, 2003) would result in the date September 12, 2017.

(e) The earlier date as determined in paragraphs (c) and (d) is August 13, 2010.

(f) Because the original patent was not issued and a request for an exemption was not submitted before September 24, 1984 and the commercial marketing or use of the product was not approved before September 24, 1984, five (5) years when added to the original expiration date of the patent (December 5, 2006) would result in the date December 5, 2011.

(g) The earlier date as determined in paragraphs (e) and (f) is August 13, 2010.

Statement Pursuant to 37 C.F.R. § 1.740 (a)(13)

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought as required under 37 C.F.R § 1.765.

The Commissioner is authorized to charge the prescribed fee under 37 C.F.R. § 1.120 (j) for receiving and acting upon this Application to Deposit Account No. 50-1986.

Please address all inquiries and correspondence relating to this Application to:

Timothy J. Douros, Esq.
Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, Massachusetts 02421
Tel.: (781) 860-8660
Fax: (781) 860-1407

A power of attorney authorizing Mr. Timothy J. Douros to act on behalf of Applicant is attached hereto as Exhibit F.

Pursuant to MPEP § 2753, this Application is being submitted as one original accompanied by four additional copies of the Application, for a total of five copies.

Respectfully submitted,

Dated: November 10, 2003

Customer No.: 34103
Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, Massachusetts 02421
Tel.: (781) 860-8660
Fax: (781) 860-1407

Timothy J. Douros
Registration No. 41,716
Attorney for Applicant
Jill M. Mandelblatt
Registration No. 37,878
Patent Agent for Applicant

Attachments

34103
PATENT TRADEMARK OFFICE

CERTIFICATE OF EXPRESS MAILING (37 CFR §1.8)

I hereby certify that this correspondence is being deposited with the United States Postal Service via Express Mail with sufficient postage in an envelope addressed to: *Mail Stop Patent Extension, Commissioner for Patents., Alexandria, VA 22313-1450* on November 10, 2003.

Name: Timothy J. Douros

Signature — November 10, 2003 Sig. Date

EXHIBIT A

Notice of Recordation of Assignment

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SEPTEMBER 29, 2003

PTAS

700045610A

CUBIST PHARMACEUTICALS, INC.
TIMOTHY J. DOUROS
65 HAYDEN AVENUE
LEXINGTON, MA 02421

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 09/25/2003

REEL/FRAME: 013998/0710
NUMBER OF PAGES: 6

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
ELI LILLY AND COMPANY

DOC DATE: 09/25/2003

ASSIGNEE:
CUBIST PHARMACEUTICALS, INC.
65 HAYDEN AVENUE
LEXINGTON, MASSACHUSETTS 02421

SERIAL NUMBER: 06773762
PATENT NUMBER: 4885243

FILING DATE: 09/09/1985
ISSUE DATE: 12/05/1989

SERIAL NUMBER: 06652695
PATENT NUMBER: 4537717

FILING DATE: 09/21/1984
ISSUE DATE: 08/27/1985

SHARON BROOKS, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

EXHIBIT B

U.S. Patent No. 4,885,243

United States Patent [19]

Huber et al.

[11] **Patent Number: 4,885,243**

[45] **Date of Patent: Dec. 5, 1989**

[54] **PROCESS FOR PRODUCING A-21978C DERIVATIVES**

[75] Inventors: **Floyd M. Huber**, Danville; **Richard L. Pieper**, Indianapolis; **Anthony J. Tietz**, Plainfield, all of Ind.

[73] Assignee: **Eli Lilly and Company**, Indianapolis, Ind.

[21] Appl. No.: **773,762**

[22] Filed: **Sep. 9, 1985**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 658,979, Oct. 9, 1984, abandoned.

[51] **Int. Cl.**[4] **C12P 21/04**; C12R 1/465; C07K 1/00

[52] **U.S. Cl.** **435/71.3**; 435/886; 530/317

[58] **Field of Search** 435/70, 71, 886; 530/317

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,288,403	6/1980	Hamill et al.	424/115
4,331,594	5/1982	Hamill et al.	435/71
4,482,487	11/1984	Abbott et al.	530/317

Primary Examiner—Elizabeth C. Weimar
Attorney, Agent, or Firm—Nancy J. Harrison; Leroy Whitaker

[57] **ABSTRACT**

An improved process for producing A-21978C cyclic peptide derivatives having a C_2–C_{14} alkanoyl side chain which comprises feeding a C_2–C_{14} alkanoic acid, or an ester or salt thereof, to the A-21978C-producing culture during the production stages of the fermentation.

11 Claims, No Drawings

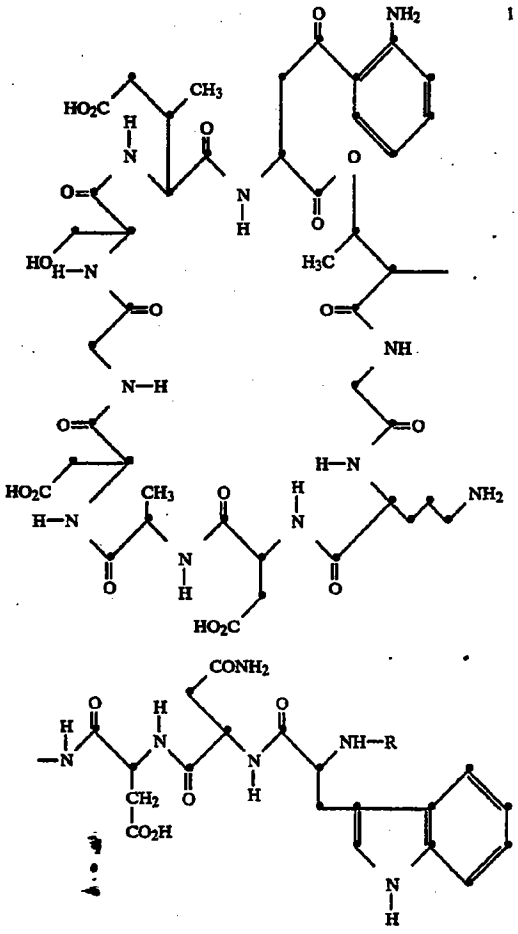
PROCESS FOR PRODUCING A-21978C DERIVATIVES

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of copending application Ser. No. 658,979, filed Oct. 9, 1984, now abandoned.

SUMMARY OF THE INVENTION

This invention relates to an improved process for preparing derivatives of the A-21978C cyclic peptide antibiotics which have the formula



wherein R is C_2–C_{14}-alkanoyl. The improved process comprises feeding a C_2–C_{14}-alkanoic acid to the A-21978C producing culture during the fermentation. The advantages of this process are: (1) it requires fewer steps than the current process, (2) the product yield is increased; and (3) it requires less time.

DETAILED DESCRIPTION OF THE INVENTION

The A-21978C antibiotics are excellent antibacterial agents. A particularly important group of A-21978C derivatives are those having formula 1 (see Bernard J. Abbott, David S. Fukuda and Manuel Debono, U.S. Pat. No. 4,537,717, which will issue Aug. 27, 1985). Previously, preparation of these derivatives required a multistep process, which was time-consuming, yield-consuming and expensive. This invention provides an improved process for making these A-21978C derivatives directly. The prior process for preparing a formula 1 derivative, such as the n-decanoyl derivative of A-21978C, required the following steps:

1. Fermentation of the A-21978C-producing culture.
   a. Initiating with a liquid nitrogen ampoule.
   b. Primary inoculum stage (48 hours).
   c. Secondary inoculum stage (24 hours).
   d. Tertiary inoculum stage (24 hours).
   e. Fermentation (140 hours).
2. Filtration, resin adsorption and elution, and concentration.
3. Preparation of t-Boc complex.
4. Concentration of the complex.
5. Fermentation of the deacylating culture, e.g. *Actinoplanes utahensis.*
   a. Initiating with a liquid nitrogen ampoule
   b. Primary inoculum stage (72 hours)
   c. Secondary inoculum stage (48 hours)
   d. Fermentation (67 hours)
6. Deacylation of the complex with the deacylating culture.
7. Filtration, resin adsorption and elution, and concentration.
8. Reacylation.
9. Hydrolysis of the protecting group.
10. Final purification.

The novel process of this invention comprises adding a C_2–C_{14} alkanoic acid (an ROH compound wherein R is as defined supra), or an ester or salt thereof, to an A-21978C-producing culture during the production stage of the fermentation (step 1e) to give the corresponding formula 1 compound. With this process, steps 3, 4, 5, 6, 7, 8 and 9 of the previous process can be eliminated. In addition, the new process substantially increases the yields obtained over those obtained using the previous process.

Streptomyces roseosporus strains NRRL 11379 and NRRL 15998, a mutant strain of NRRL 11379, are useful A-21978C-producing cultures. These cultures are part of the stock culture collection of the Northern Regional Research Center, U.S. Department of Agriculture, Agricultural Research Service, Peoria, Ill. 61604, from which they are available to the public under the accession numbers NRRL 11379 and NRRL 15998. The *S. roseosporus* NRRL 11379 culture and conditions for its use in the production of the A-21978C antibiotics are described by Robert L. Hamill and Marvin M. Hoehn in U.S. Pat. No. 4,331,594, incorporated herein by reference.

The naturally occurring A-21978C factors described in U.S. Pat. No. 4,331,594 are factors C_0, C_1, C_2, C_3, C_4 and C_5. In factors C_1, C_2, C_3, C_4 and C_5, the R in formula 1 is a specific C_{10}–C_{12}-alkanoyl group. A-21978C factor C_0, earlier thought to have a unique branched C_{10}-alkanoyl side chain, has been found to be a mixture of two components in approximately a 2:1 ratio. The major component has a branched-C_{10}-side chain, and the minor component has the straight-C_{10}-side chain.

For convenience in discussions herein when a formula 1 compound is prepared by the process of this invention, it is also called an A-21978C factor. Except for the naturally occurring factors, the length of the side

chain is used to designate the factor. Thus, for example, the formula 1 compound wherein R=octanoyl, when prepared by this process is called an A-21978C$_8$ factor.

In the C_2–C_{14} alkanoic acid, ester or salt (the substrate) used in the process of this invention, the alkyl portion can be a straight or branched chain. To prepare the naturally occurring A-21978C factors C_1, C_2 or C_3, for example, an 8-methyldecanoic, 10-methyldodecanoic or 10-methylundecanoic acid, ester or salt would be used. The C_2–C_{14} straight-chain acids, esters and salts are recommended for use in the process because of their availability and lower cost. An especially preferred substrate is n-decanoic acid and its esters and salts.

When using a C_2–C_{14} alkanoic acid ester, the C_1–C_4-alkyl esters are preferred. In such an ester, the C_1–C_4-alkyl group may also be straight or branched.

Representative suitable salts of C_2–C_{14}-alkanoic acids which may be used in the process include those formed from alkali metals and alkaline-earth metals such as sodium, potassium, lithium, cesium, rubidium, barium, calcium and magnesium. Suitable amine salts include the ammonium and the primary, secondary and tertiary C_1–C_4-alkyl- ammonium and hydroxy-C_2–C_4-alkylammonium salts.

It is preferable to add the substrate to the fermentation in the form of a sterile solution. A particularly useful solvent for this purpose is methyl oleate, although other solvents such as ethanol, ethyl acetate and C_1–C_4 esters of unsaturated fatty acids can be used. If the substrate is suitably fluid at the fermentation temperature, it may be added directly.

The rate of addition of the substrate to the fermentation must be low enough to avoid producing a toxic effect on the fermentation, but high enough to increase the yield of the desired formula 1 compound. Rates of addition of about 0.05 to about 0.5 ml per liter of fermentation broth per hour are recommended. A rate of from about 0.1 to about 0.2 ml per liter of fermentation broth per hour is preferred.

The substrate is added to the growing A-21978C-producing culture during the production stage of the fermentation, beginning at from about 15 to about 32 hours and continuing until the fermentation is terminated. The substrate can be added by various methods. It is preferable, however, to add it by a method which best approaches a steady flow.

Following the fermentation, the desired formula 1 compound, which is produced as an A-21978C factor (as defined, supra), can be recovered using procedures known in the art (see, e.g., U.S. Pat. No. 4,331,594).

The formula 1 compounds are excellent antibacterial agents.

In order to illustrate more fully the operation of this invention, the following examples are provided.

EXAMPLE 1

Production of the A-21978C Complex

A stock culture is prepared and maintained in the vapor phase of liquid nitrogen. *Streptomyces roseosporus* NRRL 15998 previously stored in the vapor phase of liquid nitrogen was used to inoculate 50 ml of vegetative medium of the following composition:

Ingredient	Amount (%)
Trypticase Soy Broth[a]	3.0
Dextrin	2.5
Water (deionized)	94.5

[a]Baltimore Biological Laboratories, Cockeysville MD.

The inoculated medium was incubated in a 250-ml Erlenmeyer flask at 30° C. for 48 hours on a shaker rotating through an arc of two inches at 250 RPM. The mature vegetative culture was dispensed into multiple containers (0.5 ml/container) and stored in the vapour phase of liquid nitrogen.

In order to provide a larger uniform supply of stored material, one ml of the culture stored in liquid nitrogen was used to inoculate 80 ml of the vegetative medium described above. The inoculated vegetative medium was incubated in a 250-ml Erlenmeyer flask at 30° C. for 48 hours on a shaker rotating through an arc two inches in diameter at 250 RPM.

Ten ml of such a culture was used to inoculate 450 ml of a second-stage vegetative growth medium having the same composition as the primary vegetative medium described supra. The second-stage medium was incubated in a 2-liter Erlenmeyer flask for 24 hours at 30° C. on a shaker rotating through an arc of 2 inches at 250 RPM.

One liter of the second-stage vegetative culture was used to inoculate 39 liters of sterile tertiary inoculum development medium having the following composition:

Ingredient	Amount (%)
Soybean Flour	0.5
Yeast Extract[a]	0.5
Calcium Gluconate	1.0
KCl[b]	0.02
$MgSO_4 \cdot 7H_2O$[b]	0.02
$FeSO_4 \cdot 7H_2O$[b]	0.0004
Sag 471 (antifoam)[c]	0.03
Water	97.9296

[a]Difco Laboratories, Detroit MI

[b]Trace minerals were prepared as follows: $FeSO_4 \cdot 7H_2O$ (7.6 g) was dissolved in conc. HCl (76 ml). $MgSO_4 \cdot 7H_2O$ (380 g), KCl (380 g) and deionized water were added to bring the total volume to 3800 ml. To provide the specified minerals, use 80 ml of solution per 39 liters of tertiary inoculum development stage.

[c]Union Carbide, Danbury CT.

The inoculated medium was incubated 24 hours in a stainless steel vessel at 30° C. The vessel was aerated with sterile air at 0.85 v/v/m and stirred with conventional agitators at 350–450 RPM. The pressure on the vessel was maintained at 5 PSIG.

One liter of the incubated tertiary inoculum stage was used to inoculate 119 liters of sterile production medium having the following composition:

Ingredient	Amount (%)
Soybean Flour	2.2
$Fe(NH_4)_2SO_4 \cdot 6H_2O$	0.066
Dextrose	0.825
Sag 471	0.022
Potato Dextrin	3.3
Molasses (blackstrap)	0.275
Tap Water	93.312

The pH was adjusted to 7.0 after addition of the first two ingredients and again after addition of all the ingredients immediately prior to sterilization.

The inoculated production medium was incubated 6 days in a stainless steel vessel at 30° C. and aerated with sterile air at a rate of 0.5 v/v/m. The medium was stirred with conventional agitators at 250 RPM from 0 to 15 hours and at 350 RPM after 15 hours. The pH was maintained at or above 6.5 by addition of ammonium hydroxide solution. The yield of A-21978C complex was 0.282 grams per liter of broth at the end of the fermentation. The factor distribution is described in Table 1.

EXAMPLE 2

Enhanced Production of A-21978C_8

The primary, secondary, and the tertiary growth stages were carried out as described in Example 1. The production stage was initiated as described in Example 1 except, beginning at 28 hours a sterile solution consisting of 50% v/v caprylic (octanoic) acid and methyl oleate was fed to the fermentation at a rate of 0.13 ml per liter of fermentation broth per hour and maintained at this rate until termination of the fermentation at 144 hours. The yield of A-21978C complex was 1.255 grams per liter of broth, a 445% increase in yield over that in Example 1. Factor A-21978C_8 (the formula 1 compound wherein R=octanoyl) represented 9% of the total A-21978C complex prepared by this method; no A-21978C_8 was detected in A-21978C complex prepared by the method of Example 1.

EXAMPLE 3

Enhanced Production of A-21978C_9

The primary, secondary and tertiary inoculum development stages were carried out as described in Example 1. The production stage was initiated as described in Example 1 except, beginning at 28 hours, a sterile solution consisting of 25% v/v nonanoic acid, and 75% methyl oleate was fed to the fermentation at a rate of 0.13 ml per liter of fermentation broth per hour and maintained at this rate until termination of the fermentation at 144 hours. The yield of A-21978C complex was 0.821 grams per liter of broth, a 293% increase over that obtained in Example 1. Factor A-21978C_9 (formula 1: R=nonanoyl) represented 10% of the total A-21978C complex prepared by this method; no A-21978C_9 was detected in the A-21978C complex prepared by the method of Example 1.

EXAMPLE 4

Enhanced Production of A-21978C_{10} Factor (formula 1: R=n-decanoyl)

The primary and second stage vegetative growth stages were cultured as described in Example 1. In the tertiary stage 800 ml of secondary inoculum culture were used to inoculate 950 liters of sterile tertiary inoculum development medium having the following composition:

Ingredient	Amount (%)
Dextrose	2.0
Calcium Carbonate	0.2
Soybean Flour	2.0
Yeast Extract	0.1
KCl[a]	0.02
$MgSO_4 \cdot 7H_2O$[a]	0.02
$FeSO_4 \cdot 7H_2O$[a]	0.0004
Sag 471 (antifoam)	0.02
Water	95.6396

[a]Trace mineral solution prepared as described in Example 1.

The inoculated medium was incubated 24 hours in a stainless steel vessel at 30° C. The vessel was aerated with sterile air at a rate of 0.8 v/v/m and stirred with conventional agitators. One liter of this tertiary stage inoculum was used to inoculate 119 liters of production stage medium having the composition described in Example 1. The production stage was also initiated as described in Example 1 except, beginning at 28 hours, a sterile solution consisting of 50% v/v capric (decanoic) acid and 50% methyl oleate was fed to the fermentation at a rate of 0.26 ml per liter of fermentation broth per hour and maintained at this rate until termination of the fermentation at 283 hours. The yield of A-21978C complex was 1.94 grams per liter of broth, a 687% increase over that obtained in Example 1. The concentration of the A-21978C_{10} factor (formula 1: R=n-decanoyl) was 1.63 grams per liter or 84% of the total A-21978C complex. This was 13583% greater than the amount of A-21978C_{10} produced using the Example 1 procedure.

EXAMPLE 5

Alternate Method of Enhanced Production of A-21978C_{10}

The primary, secondary, and tertiary inoculum development stages were carried out as described in Example 1. The production stage was initiated as described in Example 1 except, beginning at 28 hours, a sterile solution consisting of 25% v/v capric acid ethyl ester (ethyl caprate) and 75% methyl oleate was fed to the fermentation at a rate of 0.13 ml per liter of fermentation broth per hour and maintained at this rate until termination of the fermentation at 144 hours. The yield of A-21978C complex was 1.022 grams per liter, a 362% increase over that obtained in Example 1. The concentration of factor A-21978C_{10} was 0.202 grams per liter or 20% of the total A-21978C complex. This was 1683% greater than the concentration of A-21978C_{10} produced using the method of Example 1.

EXAMPLE 6

Alternate Method for Enhanced Production of A-21978C_{10}

The primary and second stage vegetative growth stages were cultured as described in Example 1. The tertiary stage inoculum was cultured as described in Example 4 except that the volume of medium was 1900 liters and the duration of the stage was extended to 48 hours. The aeration rate was 0.3 v/v/m from 0 to 24 hours, 0.45 v/v/m from 24 to 40 hours and 0.90 v/v/m from 40 to 48 hours. The production stage was initiated as described in Example 1. At 23 hours a sterile slurry of 0.004% yeast extract was batch fed to the fermentation. Beginning at 36 hours, a solution of glycerol and ammonium decanoate was fed at a rate of 0.84 ml per liter of fermentation broth per hour. The feeding solution contained glycerol (3600 g), deionized water (9000 ml), capric acid (1 liter), and concentrated ammonium hydroxide solution (620 ml). The feed was maintained at this rate until the fermentation was terminated at 143 hours. The yield of A-21978C complex was 1.772 grams per liter, a 628% increase over that obtained in Example

1. The concentration of factor A-21978C_{10} was determined to be 0.739 grams per liter or 42% of the total A-21978C complex. This was 6158% greater than the concentration of A-21978C_{10} when produced by the method of Example 1.

EXAMPLE 7

Enhanced Production of A-21978C_{11}

The primary, secondary, and tertiary inoculum stages were carried out as described in Example 1. The production stage was initiated as described in Example 1 except, beginning at 28 hours, a sterile solution consisting of 25% v/v undecanoic acid and 75% methyl oleate was fed to the fermentation at a rate of 0.13 ml per liter of fermentation broth per hour until termination of the fermentation at 144 hours. The yield of A-21978C complex was 1.62 grams per liter, a 574% increase over that obtained in Example 1. The concentration of factor A-21978C_{11} (formula 1: R=undecanoyl) was determined to be 0.70 grams per liter or 43% of the total A-21978C complex. Factor A-21978C_{11} could not be detected in the A-21978C complex prepared by the Example 1 method.

EXAMPLE 8

Enhanced Production of A-21978C_5

The primary, secondary, and tertiary inoculum stages were carried out as described in Example 1. The production stage was initiated as described in Example 1 except, beginning at 28 hours, a sterile solution consisting of 25% v/v lauric acid and 75% methyl oleate was fed to the fermentation at a rate of 0.13 ml per liter of fermentation broth per hour until termination of the fermentation at 144 hours. The yield of A21978C complex was 1.12 grams per liter, a 400% increase over that obtained in Example 1. The concentration of factor A-21978C_5 (formula 1: R=dodecanoyl) was determined to be 0.372 grams per liter or 33% of the total A-21978C complex. This was 5314% greater than the concentration of A-21978C_5 found in A-21978C complex produced by the method of Example 1.

TABLE 1

EFFECT OF VARIOUS LIPID SUBSTRATES ON THE PRODUCTION of A-21978C COMPONENT

Example	Lipid Substrate	A-21978C Component(μg/ml)[a,b] C_1	C_2	C_3	C_5	C_8	C_9	C_{10}	C_{11}
1	None	77	113	72	7	—	—	12[c]	—
2	Caprylic Acid	276	312	214	175	113	—	170	—
3	Nonanoic Acid	147	177	125	192	—	83	90	—
4	Capric Acid	135	50	48	77	—	—	1630[d]	—
5	Capric Acid Ethyl Ester	168	246	156	251	—	—	202[d]	—
6	Ammonium Decanoate	335	371	228	98	—	—	739[d]	—
7	Undecanoic Acid	163	206	158	273	—	—	118	700
8	Lauric Acid	204	236	141	372	—	—	173	—

[a]The concentration of the antibiotic components in filtered broth was estimated by high performance liquid chromatography; the various components were detected by ultraviolet light absorption.

[b]C_0, C_1, C_2, C_3 and C_5 = naturally occurring A-21978C factors; C_8, C_9, C_{10} and C_{11} = formula 1 compounds wherein R = C_8, C_9, C_{10} and C_{11} acryl groups, respectively.

[c]Natural factor C_0

[d]found to be substantially R = n-decanoyl

EXAMPLE 9

Alternate Production of the A-21978C Complex

A-21978C complex is produced using the procedure of Example 1, but the *Streptomyces roseosporus* NRRL 11379 culture is used.

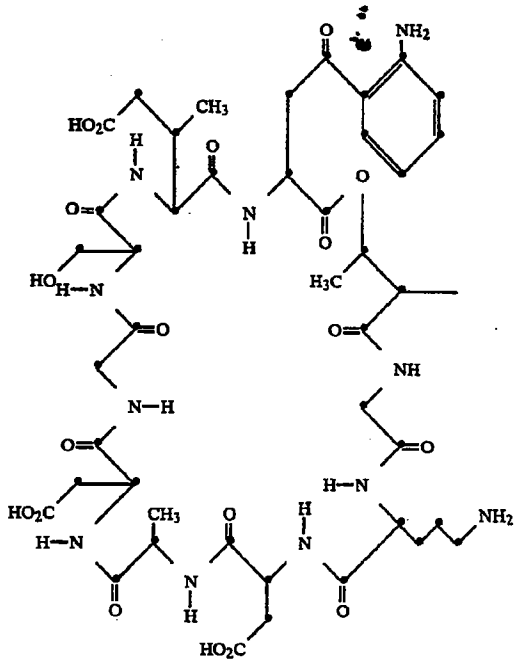
EXAMPLE 10

Alternate Method for Enhanced A-21978C_{10} Production

A-21978C_{10} is produced using the method of Example 6, but the *Streptomyces roseosporus* NRRL 11379 culture is used.

We claim:

1. In the process for producing an A-21978C derivative of the formula



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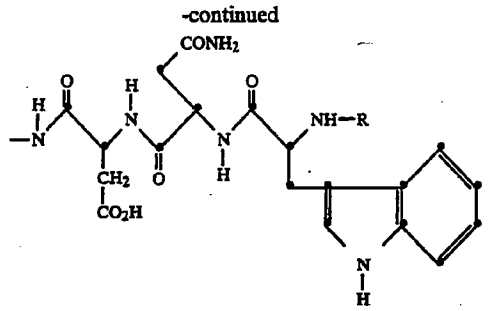

wherein R is a C_2–C_{14}-alkanoyl group, the improvement which comprises feeding the corresponding ROH acid, or an ester or salt thereof, to an A-21978C-producing *Streptomyces roseosporus* culture selected from NRRL 11379, NRRL 15998, or an A-21978C-producing mutant thereof, during the production stage of the fermentation until the A-21978C derivative is produced.

2. The process of claim 1 wherein a C_2–C_{14}-alkanoic acid is used.

3. The process of claim 1 wherein a C_1–C_4-alkyl ester of a C_2–C_{14}-alkanoic acid is used.

4. The process of claim 1 wherein a salt of a C_2–C_{14}-alkanoic acid is used.

5. The process of claim 2 wherein the alkanoic acid is caprylic acid.

6. The process of claim 2 wherein the alkanoic acid is nonanoic acid.

7. The process of claim 2 wherein capric acid is used.

8. The process of claim 3 wherein capric acid ethyl ester is used.

9. The process of claim 4 wherein ammonium decanoate is used.

10. The process of claim 2 wherein undecanoic acid is used.

11. The process of claim 2 wherein lauric acid is used.

* * * * *

EXHIBIT C

Maintenance Fee Records for U.S. Patent No. 4,885,243

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Maintenance Fee Statement

4885243

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,885,243	183	930	0	06/773,762	12/05/89	09/09/85	04	NO	PAID

ITEM NBR	ATTY DKT NUMBER
1	X-6459A

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ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,885,243	184	2050	0	06/773,762	12/05/89	09/09/85	08	NO	PAID

ITEM NBR	ATTY DKT NUMBER
1	X-6459A

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ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,885,243	185	2990	0	06/773,762	12/05/89	09/09/85	12	NO	PAID

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ITEM NBR	ATTY DKT NUMBER
1	X-6459A

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Patent Number: 4885243 **Application Number:** 06773762

	4th Year	8th Year	12th Year
Opening	12/07/1992	12/05/1996	12/05/2000
Surcharge	06/08/1993	06/06/1997	06/06/2001
Closing	12/06/1993	12/05/1997	12/05/2001

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EXHIBIT D

Chronology of Events Concerning IND 27,627

Lilly IND Log – IND #27,627

Date	Submission Number	Source	Activity
December 20, 1985	000	Lilly	Initial IND submission, including pre-clinical, CMC, microbiological, general investigational plan, and initial clinical trial for Gram-positive infections
February 20, 1986		Lilly	FDA/Lilly meeting to discuss Lilly initial core clinical protocol utilizing daptomycin *vs.* conventional therapy in Gram-positive infections (including skin and skin structure). Also a presentation was made regarding an additional clinical protocol for surgical prophylaxis.
March 5, 1986		Lilly	A summary of the joint FDA/Lilly meeting on February 20, 1986 was provided as well as an update to the initial daptomycin *vs.* conventional therapy protocol
April 21, 1986		FDA	Anti-Infective Division members provide additional comments to the protocol submitted on March 5, 1986 and further suggest requirements for bioavailability studies to be conducted in normal volunteers.
June 19, 1986		Lilly	Lilly provides FDA with protocol 85-042; bioavailability study of several singl intravenous doses of daptomycin with supporting documentation to study design.
July 9, 1986		Lilly	Updates to the intravenous bioavailability study provided to FDA.
September 30, 1986		Lilly	Final reports on teratology in rats and rabbits submitted to the Agency.
October 15, 1986		Lilly	A final report of the bioavailability study is supplied by Lilly to the FDA.
October 16, 1986		Lilly	Lilly provides a ^{14}C radio-labelled distribution and metabolism study report in various animal species.
November 19, 1986		Lilly	Provides FDA with an updated CMC amendment modifying the daptomycin formulation which will not contain mannitol.

Date	Submission Number	Source	Activity
December 22, 1986		Lilly	Additional chemical manufacturing and control data is submitted to the Agency. This is information inadvertently omitted from previous amendments. In addition, the Annual report for this IND is submitted.
January 9, 1987		Lilly	Protocol B8B-MC-AVAD is submitted to the Agency. This study is designed to determine the safety and disposition of daptomycin following IV doses of 1 mg/kg in normal subjects and patients with renal insufficiency.
February 3, 1987		Lilly	Protocol B8B-LC-AVAF is submitted to the Agency. This study is to establish daptomycin dose linearity between 0.5 and 2.0 mg/kg.
February 18, 1987		Lilly	Lilly submits an 18-week basic fertility study of daptomycin in rats.
March 9, 1987		Lilly	Protocol B8B-MC0AVAE is submitted to evaluate Gram-positive infections utilizing daptomycin.
March 25, 1987		Lilly	Lilly submits two *in vitro* studies to examine any potential gene mutations.
March 30, 1987		Lilly	Lilly submits protocol B8B-LC-AVAI, a safety, tolerance and steady state pharmacokinetic study for the use of daptomycin at 2 mg/kg for 14 days.
April 16, 1987		Lilly	Lilly submits an updated Investigator's Brochure for daptomycin.
May 19, 1987		Lilly	Lilly submits protocol B8B-LC-AVAI. This study was designed to evaluate potential drug-drug interactions when tobramycin is given concomitantly with daptomycin in humans.
May 26, 1987		Lilly	Lilly submits two preliminary animal studies evaluating the potential interaction of daptomycin and tobramycin in dogs and rats.
May 29, 1987		Lilly	Lilly submits a pre-meeting package and planned agenda for a joint Lilly and FDA meeting targeted for June 16, 1987.
July 6, 1987		Lilly	Lilly submits Amendment Number 1 to protocol B8B-MC-AVAE.

Date	Submission Number	Source	Activity
July 8, 1987		Lilly	Lilly provides an information amendment which includes updated information on the stability of reconstituted daptomycin.
July 9, 1987		Lilly	Lilly submits the final report for clinical study B8B-LC-AVAC; the distribution of ^{14}C daptomycin.
July 15, 1987		Lilly	Lilly amends the active daptomycin IND with a 3-month subchronic dog toxicity study.
July 16, 1987		Lilly	Lilly provides FDA with a revised version for tracking clinical investigators as a result of discussion held June 16, 1987.
July 30, 1987		Lilly	Provides FDA with an updated clinical investigator listing for protocol AVAE.
August 13, 1987		Lilly	Provides FDA with a final report to clinical study B8B-LC-AVAI.
August 27, 1987		Lilly	Provides FDA with a final report to clinical study B8B-LC-AVAF.
September 24, 1987		Lilly	Lilly amends the active daptomycin IND with a revised copy of protocol B8B-MC-AVAE and a list of newly participating investigators.
September 24, 1987		FDA	The agency requests submission of stability testing results as a percentage of label potency.
October 2, 1987		Lilly	Lilly submits a revised version of the Clinical Investigator's Brochure to the Agency. Also submitted is an *in vitro* pre-clinical safety report evaluating the mutagenicity potential of daptomycin.
November 30, 1987		Lilly	Lilly amends the currently active IND with an update to the CMC information. This amendment is in response to the FDA correspondence of September 24, 1987.
December 14, 1987		FDA	The Agency requests that Lilly should set a limit for moisture and mannitol content in the current daptomycin formulation.
December 17, 1987		Lilly	Lilly Amends the currently active daptomycin IND with the 1987 Annual Report.

Date	Submission Number	Source	Activity
January 11, 1988	001	Lilly	Lilly amends the current IND with an update/correction to the clinical study B8B-LC-AVAJ final report.
January 18, 1988	002	Lilly	Lilly files a Serious Adverse Event Report of a septic death in a woman with heart disease and valve prosthesis still positive to *Staphylococcus aureus* 3 days after initiating treatment.
February 19, 1988	005	Lilly	Lilly submits CMC amendment in response to question raised by the Agency on December 14, 1987.
March 8, 1988	006	Lilly	Lilly submits an *in vitro* study final report regarding an evaluation of the potential interaction between daptomycin and aspirin.
May 19, 1988	010	Lilly	Lilly amends the active IND with a chronic toxicity study of 6 months duration in rats.
June 2, 1988	011	Lilly	Lilly submits a letter to the Agency informing them that Lilly is temporarily placing clinical trials on hold due to less than expected efficacy.
July 13, 1988		Lilly	Lilly provides the Agency with correspondence to confirm a joint meeting scheduled for July 19, 1988, along with a preparatory briefing package for that meeting.
July 18, 1988	014	Lilly	Lilly submits a chronic toxicity study in beagle dogs of 6 month duration to the active IND.
August 15, 1988	015	Lilly	Lilly amends the IND with protocol B8B-LC-AVAK, a dose linearity study for daptomycin.
August 22, 1988	017	Lilly	Lilly amends the active IND with an *in vitro* pre-clinical study report evaluating daptomycin in the neuromuscular junction.
August 23, 1988	018	Lilly	Lilly provides FDA with their version of meeting minutes to the July 19, 1988 joint meeting.

Date	Submission Number	Source	Activity
September 14, 1988	019	Lilly	Lilly provides FDA with a synopsis of a September 9, 1988 telephone conversation where agreement was reached for Lilly to re-initiate clinical trials and escalate the dose for desired efficacy and safety assessment.
October 14, 1988	020	Lilly	Lilly updates protocol B8B-LC-AVAK based on discussion between the two parties on September 9, 1988.
November 3, 1988		FDA	FDA response to protocol updates submitted on October 14, 1988 and requests expansion of the neuromuscular safety assessment.
November 23, 1988	021	Lilly	Lilly submits final report for clinical trial in daptomycin *vs.* conventional therapy in Gram-positive infections.
December 5, 1988	022	Lilly	Lilly amends the active IND with the daptomycin Annual Report.
March 29, 1989	023	Lilly	Lilly amends the current IND with a final report to clinical study B8B-LC-AVAK, a revised clinical investigator's brochure and two new protocols: B8B-MC-AVAM and B8B-MC-AVAL. These studies are designed to determine the *in vivo* bind of daptomycin in human serum and to evaluate daptomycin in seriously ill patients with bacteremia and/or endocarditis.
May 18, 1989	025	Lilly	Lilly amends the current IND with a pre-clinical acute dermal and ocular study to support environmental safe handling.
October 12, 1989	029	Lilly	Lilly amends clinical protocol B8B-MC-AVAM. This amendment changes the algorithm for the treatment of endocarditis bacteremia by the potential of adding an aminoglycoside to the treatment regimen.
December 14, 1989	034	Lilly	Lilly amends the current IND with the daptomycin 1989 annual report.
May 25, 1990	039	Lilly	Lilly amends protocol B8B-MC-AVAM to obtain pharmacokinetics in bacteremia and endocarditis patients.
June 1, 1990	040	Lilly	Lilly submits correspondence to FDA requesting a meeting to review End of Phase II data.

Date	Submission Number	Source	Activity
July 25, 1990	045	Lilly	Lilly submits correspondence to the Agency confirming the joint scheduled meeting for August 8, 1990. A pre-meeting package was also submitted as a prelude to the scheduled meeting.
August 10, 1990	047	Lilly	Lilly amends the active IND with 8-month fertility, prenatal and postnatal studies in rats.
August 22, 1990	049	Lilly	Lilly submits meeting minutes to the August 8, 1990 jointly held End of Phase II review for daptomycin. Additional analysis was requested of some Phase II data by the Agency. Additional Phase II/III studies could proceed.
September 6, 1990	052	Lilly	This correspondence documented the follow-up meeting between Lilly and FDA conducted on August 23, 1990. The follow-up was the the earlier joint meeting held August 8, 1990. This meeting was conducted to evaluate a draft protocol for daptomycin 5 mg/kg q12hrs in endocarditis and how the endocarditis evaluation should proceed.
September 24, 1990	054	Lilly	Lilly amends the IND with correspondence documenting the agreed-upon issues in regard to patient treatment of endocarditis and evaluation of neurologic monitoring from the two previous joint meetings.
October 29, 1990	056	Lilly	Lilly provided correspondence summarizing the agreements reached with FDA in a joint teleconference on October 10, 1990. Documented was that Lilly would proceed with the Phase I PK trial to evaluate daptomycin doses between 3 and 5 mg/kg q12hr for 14 days. Lilly would also finalize a protocol to treat endocarditis and bacteremia patients with daptomycin at a dose of 3 mg/kg q12hrs escalating up to 10 mg/kg/day.

Date	Submission Number	Source	Activity
December 3, 1990	058	Lilly	Lilly submits documentation to a joint FDA/Lilly teleconference held November 20, 1990 noting the agreed-upon issues for the Phase II trial in endocarditis.
December 11, 1990	059	Lilly	Lilly submits a protocol amendment to study B8B-MC-AVAP incorporating the agreed-upon changes of November 20, 1990.
January 16, 1991	061	Lilly	Lilly further amends clinical study B8B-MC-AVAP.
March 8, 1991	064	Lilly	Lilly informs the Agency that they have voluntarily suspended further evaluation of daptomycin in clinical trial B8B-MC-AVAM due to marked CPK elevations at the 4 mg/kg q12hr treatment regimen.
April 3, 1991		FDA	With reference to the above Lilly communication, FDA places all human studies with daptomycin on clinical hold.
August 19, 1991	067	Lilly	Lilly submits pre-clinical safety studies for ototoxicity evaluation and a 3-month continuous trial of daptomycin in rats.
December 12, 1991	068	Lilly	Lilly submits a series of pre-clinical studies on tissue distribution and elimination of daptomycin in rats.
December 17, 1991	072	Lilly	Lilly provides correspondence to FDA requesting the daptomycin IND be placed on an inactive status without prejudice.
December 19, 1991	069	Lilly	Lilly submits the daptomycin Annual Report.
January 29, 1992		FDA	FDA correspondence to Lilly indicating that daptomycin IND is considered to be on inactive status.

EXHIBIT E

Chronology of Events Concerning IND 57,693 and NDA 21-572

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3/8/91 Lilly	Letter to FDA from M. W. Talbott (Director, Medical Affairs, Eli Lilly) informing the Agency that Eli Lilly has voluntarily suspended further evaluations of Daptomycin in study B8B MC AVAM due to mark CPK elevations. (Re: IND# 27,627)
4/3/91 FDA	Letter from FDA informing Lilly that all studies on humans are put on Clinical Hold pursuant to 21 CFR 312.42
12/15/97 Cubist	Summary of teleconference with FDA to discuss process of reopening of Daptomycin IND previously held by Eli Lilly.
12/22/97 Cubist	Summary of 12/19/97 teleconference with Frances LeSane (CSO) re: reopening of Daptomycin IND.
12/22/97 Cubist	Letter to Frances LeSane (CSO) as follow-up to 12/19/97 teleconference; request to reopen Lilly's Daptomycin IND; request meeting to review daptomycin clinical program. Enclosed: • Lilly's licensing agreement with Cubist • Clinical hold letter from M. Lumpkin (FDA) to M. Talbott (Lilly) 4/3/91. • Outline of Clinical Program and Rationale
12/23/97 Cubist	Summary of voice-mail to Dr. Albuerne (Head Medical Reviewer) by Frank Tally re: package sent to Frances LeSane to reopen Lilly IND, noting Licensing Agreement and Cubist's interest in an early meeting with FDA to discuss overall clinical plans and rationale.
1/28/98 Cubist	Fax to Frances LeSane in preparation for teleconference scheduled 1/29/98 or 2/2/98. Enclosed: • Brief summary of Daptomycin background and rationale for proposed clinical program/removing Lilly clinical hold.
2/2/98 Cubist	Summary of 2/2/98 teleconference with FDA Daptomycin IND team: Cubist to file its own IND and cross-reference Lilly IND; FDA requests pre-IND package; discussion of actions required of Cubist prior to meeting at FDA; focus of effort to be pre-IND document.
3/12/98 Cubist	Letter to Dr. Chikami articulating Cubist's general clinical plan, requesting April 1998 pre-IND meeting, and announcing Cubist's intention, after initiating intravenous program, to pursue oral administration program with its own IND. Enclosed: • Pre-IND package *Pre-IND package with Regulatory file copy*
4/16/98 Cubist	Letter to Dr. Chikami; re: 5/13/98 pre-IND meeting; announces modifications in overall clinical program; enumerates modifications. Enclosed: • Synopsis of Protocol SSS-9801 • Synopsis of Protocol UTI-9802 • Synopsis of Protocol SSS-9801A

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4/27/98 Cubist	Letter to Dr. Chikami enclosing: • Draft Protocol SSS-9801 • Updated Synopses of Protocols SSS-9801, UTI-9801, and SSS-9801A ***Protocols with Regulatory file copy.***
4/28/98 Cubist	Fax to Jose Cintron (CSO), enclosing: • Revised and updated Clinical Pharmacology Summary for pre-IND
4/29/98 Cubist	Minutes of 4/29/98 teleconference with FDA to discuss Agency's internal review of Cubist's pre-IND package. ***Discussion includes: Lilly's clinical hold will not apply to Cubist; Dr. Moledina (Medical reviewer) wants Cubist on fast track (6-9 months) review***
4/30/98 FDA	Fax from Jose Cintron (CSO) forwarding: • Comments of Microbiologist Reviewer, Dr. Marsik, dated 4/22/98
5/4/98 FDA	Fax from Jose Cintron (CSO) stating that the Toxicology Reviewer, Dr. Terry Peters, requests that Cubist conduct a segment I and segment II reproductive toxicology study before initiating Phase III clinical trials. Also that Segment III necessary prior to NDA submission. Handwritten note added by Rick Oleson re: subsequent teleconference with Jose Cintron (FDA); note indicates Dr. Peters may have overlooked reproductive toxicology reports in pre-IND; information may satisfy requirement.
5/6/98 Cubist	Fax to Jose Cintron responding to Toxicology Reviewer's (Dr. Peters) request, enclosing: • Study summaries and tables for completed Lilly reproductive toxicity studies – Toxicology Report Nos. 19, 20, 21, and 31.
5/12/98 Cubist	Letter to FDA summarizing Cubist's understanding of 4/29/98 teleconference with FDA requesting FDA to initial letter and return as confirmation of agreements.
5/13/98 Cubist	Letter to Jose Cintron enclosing: • Desk copies of reproductive toxicology study reports for review by Dr. Peters – Toxicology Report Nos. 19, 20, 21, and 31.
5/26/98 FDA	Fax from Jose Cintron attaching: • Comments of Team Leader Biopharmaceuticals, Dr. Pelsor
6/10/98 Cubist	Fax to Jose Cintron requesting teleconference with FDA to discuss Agency's comments regarding revised clinical program. Enclosed: Daptomycin: Revised Intravenous Clinical Program with Rationale

6/25/98 Cubist	Fax letter to Jose Cintron in preparation for 7/9/98 internal FDA meeting and 7/21/98 Cubist-FDA meeting. Enclosed: • Daptomycin: Revised Intravenous Clinical Program, Version 2 (6/25/98)
7/8/98 Cubist	Fax to Jose Cintron in preparation for Cubist's 7/21/98 meeting with FDA to discuss revised clinical program, including attendees, objectives, proposed agenda, key issues.
7/9/98 Cubist	Letter to Jose Cintron responding to FDA invitation to attend the 7/28/98 FDA/Industry meeting regarding clinical development of anti-infectives for treatment of resistant organisms; F. Tally and R. Oleson to attend.
7/17/98 Cubist	Letter to Jose Cintron enclosing: • Slides and references cited in slides for Cubist presentation at the Daptomycin FDA meeting on 7/21/98
07/21/98 Cubist	The Reissuance of the minutes for the July 21, 1998 meeting with the Agency
10/8/98 Cubist	Fax to Jose Cintron forwarding draft letter to Dr. Chikami requesting meeting in November to discuss clinical program. Enclosed: • Proposed agenda for requested Cubist-FDA meeting • Questions for Discussion for requested Cubist-FDA meeting
10/16/98 Cubist	Letter to Dr. Chikami requesting a November meeting to discuss trial designs with FDA and a subsequent meeting to discuss CMC section. Draft CMC section to be forwarded under separate cover. Enclosed: • Daptomycin Clinical Program Information Package 10/16/98 1. Proposed Agenda and Questions for Discussion 2. Summary of Proposed Clinical Program 3. Clinical Protocol Phase III SST 4. Clinical Protocol Phase II BAC 5. Investigator's Brochure including current micro, nonclinical & clinical summaries which supercede corresponding sections in Pre-IND document *Enclosed documents with regulatory file copy*
10/20/98 Cubist	Letter to Dr. Chikami requesting meeting with FDA team members for CMC section. Enclosed: • Draft CMC section and list of CMC portions presently incomplete • Relevant Lilly IND CMC amendment *Draft Item 7 with regulatory file copy.*

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10/27/98 Cubist	Fax letter to Dr. Chikami requesting teleconference to discuss proposed changes to elinical program, including initial focus on VRE blood stream infections. Enclosed: • Daptomycin: Intravenous Clinical Program Addendum to Plan Submitted to FDA 10/16/98. • Questions for Discussion regarding revisions to clinical program • Synopsis of Protocol VRE-9805 Draft Version 2
11/3/98 FDA	Letter from Dr. Chikami acknowledging receipt of Cubist's notification to FDA of transfer of IND ownership from Lilly to Cubist and listing sponsor obligations; also notification of clinical hold to Cubist.
11/5/98 Cubist	Letter to Jose Cintron enclosing: • Completed raw data from research study of Daptomycin in dogs Study Nos. WIL339003 and WIL 339005. ***Data with Regulatory file copy.***
11/6/98 Cubist	Fax to FDA requesting comments, guidance from Dr. Chikami and Dr. Albuerne on daptomycin development for treatment of all gram-positive life-threatening infections with VRE as subset.
11/10/98 FDA	Fax from Jose Cintron enclosing: • FDA comments, questions resulting from 11/9/98 internal daptomycin meeting This communication was erroneously dated 10/10/98 by FDA; please note receipt date of 11/10/98
11/16/98 Cubist	Letter to Dr. Chikami (in response to FDA 11/3/98 letter) clarifying prior agreements with FDA that Cubist will not be held to Lilly clinical hold and will submit new IND; also announces Judy Newberne as Dir. Reg. Affairs. Enclosed: • Selected prior correspondence (FDA 11/3/98 letter; Cubist summary of 2/2/98 teleconference; Cubist 3/12/98 letter; and Cubist 5/12/98 letter)
11/16/98 Cubist	Response to FDA comments/questions dated 11/10/98. Letter to Dr. Chikami provides clarification of clinical program; Cubist asks Agency to consider original clinical proposal of 10/16/98 with some modifications. Enclosed: • Summary of current Daptomycin Intravenous Clinical Program dated 11/16/98 (noting modifications to 10/16/98 proposal) • Timeline for proposed Daptomycin clinical trials • Questions for Discussion at FDA Daptomycin protocol review meeting for Protocol Nos. SST9801 and BAC9803.

11/16/98 Cubist	Letter to Jose Cintron to forward to Dr. Peters for review. Enclosed: • Draft reports of two exploratory Daptomycin studies in dogs *Draft reports with regulatory file copy*
11/17/98 Cubist	Fax to Jose Cintron for distribution to CMC reviewers. Enclosed: • Amendment to IND 27,627 submitted by Lilly on 9/10/90. Regarding drug substance/drug product and soybean flour to yeast change in fermentation media
11/18/98 FDA	Fax from Jose Cintron, enclosing: • Comments from 11/9/98 internal FDA meeting on daptomycin clinical program 1. Dr. Brittain, Biostatistics reviewer 2. Dr. Peters, Pharm/Tox reviewer 3. Dr. Pelsor, Biopharmaceuticals reviewer (dated 5/26/98)
11/18/98 FDA Minutes Teleconference	CMC Teleconference - comparability and stability. FDA attendees: J. Cintron, and J. Timper. Cubist attendees: M. Hersey, A. Knapp, M. K. Kottke, J. Lai, J. Newberne, and R. Oleson. At conclusion, Dr. Timper states manufacturing meeting with FDA appears unnecessary, but all issues raised in this teleconference to be forwarded to FDA in writing.
11/24/98 FDA	Fax from Jose Cintron on behalf of Dr. Moledina enclosing: • Appendix IIB, page 1 of 2 on the supplemental toxicity grading for creatine phosphokinase (CPK)
11/25/98 Cubist	Fax to Jose Cintron with list of Cubist Pharmaceutical, Inc attendees and consultants who will be present at the 12/2/98 pre-IND meeting.
11/25/98 FDA Minutes of Teleconference	Clinical Program Teleconference. FDA attendees: E. Brittain, J. Cintron, K. Lin, and A. Moledina. Cubist attendees: C. Carini, A. Knapp, R. Oleson, and F. Tally. Dr. Moledina initiated teleconference to clarify and understand Cubist's proposed clinical program.
12/1/98 Cubist	Fax to Jose Cintron enclosing: • Cubist's response to 11/18/98 FDA comments on clinical program from biostatistics, pharm/tox, and biopharmaceuticals reviewers
12/2/98 FDA Pre-IND meeting minutes	FDA attendees: M. Albuerne, E. Brittain, J. Cintron, G. Chikami, D. Evansa, H. Gavrilovich, D. Katague, Lin, Marski, A. Moledina, G. Osterberg, T. Peters, and J. Timper. Cubist attendees: A. Knapp, J. Newberne, R. Oleson, and F. Tally. Consultants: C. Berman, M. Corrado, and G. Drusano. Presentation and overview of daptomycin's characteristics and proposed clinical program for filing IND

12/08/98 Cubist	Fax to Steve Trostle (back up CSO) with letter to Dr. Timper regarding CMC and enumerating information not currently ready for IND filing. Enclosed: • HPLC chromatograms for GMP Lot 99012- 005/8 (Cubist) and 431-BYO-14.05-2 • Brief history daptomycin manufacturing process
12/08/98 Minutes of Teleconference	Unofficial phone call to Jim Timper to ask about impurity guidelines related to anti-infectives.
12/08/98 Cubist	Letter to Jim Timper to inform that some information for 12/11/98 CMC teleconference was sent via fax and enclosing here by Federal Express: • Daptomycin CMC Summary Package
12/08/98 Cubist	Letter to Steve Trostle to inform that material was sent for Jim Timper for 12/11/98 CMC teleconference via fax and Federal Express.
12/09/98 Cubist	Fax to Mike Corrado, L. Boccumini, B. Dormself, G. Drusano enclosing: • FDA statistical comments to be addressed in 12/11/98 teleconference
12/10/98 Cubist	Letter to J. Powers Target Research enclosing: • IND items 5 and 10 (Previous Clinical Experience and Micro summary) (Letter to Steve Trostle In response to pre-IND meeting December 2, 1998. The following items are being sent via Federal Express: Item 3, Item 4, Item 9, and Item 10.) • FDA Cubist Teleconference Minutes on DAP SST9801 and DAP BAC9803
12/15/98 Cubist	Fax to Jose Cintron with letter to Dr. Timper. Enclosed: • Detailed analysis of the variability of the impurity profile in daptomycin for review by Mr. Timper and Dr. Peters • 7 HPLC chromatograms dapto API with summary table of API lots
12/22/98 FDA Minutes of Teleconference	CMC Teleconference. FDA attendees: J. Cintron, J. Timper and T. Peters. Cubist Attendees: M. Hersey, T. Kelleher, A. Knapp, M. Kottke, R. Oleson, F. Tally, and K. Whetstone. An overview of issues discussed in Cubist's 12/15/98 correspondence to the FDA.
12/31/98 IND	Initial Submission: • IND Application for Daptomycin in the Treatment of Complicated Skin and Soft Tissue Infections and Bloodstream (Bacteremia) Infections Unassociated with Endocarditis, Due to Gram Positive Bacteria

1/6/99 FDA	Letter from James Bona to Rick Oleson acknowledging receipt of IND on December 31, 1998 and assigning IND number of 57,693.
1/7/99 Target Research	Fax from Jill Powers with attached copy of letter from Target to Jose Cintron responding to his request for 3 additional copies of the Daptomycin IND in behalf of Cubist Pharmaceuticals.
1/21/99 IND 001	Letter to Dr. Chikami enclosing: • Certificate of Analysis for daptomycin clinical drug product, batch 800425 • Clean chromatogram for daptomycin bulk API • Certificate of Analysis for Daptomycin API batch 001/9 • Preliminary bridging tox report without histopathology
1/22/99 Cubist	Correspondence -fax to Dr. Moledina enclosing: • Proposal for a Safety/Tolerability Interim Assessment at 6mg/kg/24h
1/26/99 Cubist	Fax to Jose Cintron with copy of IND information amendment #002: Proposal for safety/tolerability interim assessment of daptomycin at 6mg/kg/24h, to arrive at Agency via Fed Ex on 1/27/99.
1/26/99 IND 002	Information Amendment Submission: • Proposal for Safety/Tolerability Interim Assessment of Daptomycin at 6mg/kg/24h
1/29/99 IND 003	• Request for termination of Lilly IND # 27,627
2/3/99 IND 004	Information Update Submission: • Two Diskettes containing Protocols DAP BAC9803, DAP-SST9801, DAP-RRC9804 and IND Investigational Plan. (One copy for Dr. Moledina and one desk copy for Jose Cintron.)
2/8/99 FDA	• Notification that withdrawal procedure is complete for Lilly Daptomycin IND.
2/12/99 FDA	Fax from Jose Cintron enclosing: • Statistical Comments, Dr. Brittain, daptomycin protocol SST9801, BAC9803, and RRC9804.
3/11/99 IND 005	• General Correspondence: Cubist's request for brand name Daptiva

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4/7/99 Cubist — Summary of teleconference between Jose Cintron, FDA, and Andy Knapp re: FDA's directive to Dr. Subauste to submit IND in regard to patient he had treated with daptomycin on an emergency use basis.

4/9/99 IND 006 — Information Update: Addition of Investigators

	Protocol DAP-SST9801	
John Carroll, MD	Maricopa Medical Center	DAP SST9801
Jordan B. Glaser, M.D.	Staten Island University Hospital	DAP SST9801
Stephen L. Green, M.D.	Riverside Regional Medical Center	DAP SST9801
Robert S. Jones, DO	Berks Infectious Disease Services	DAP SST9801
John W King	Louisiana State University Medical Center	DAP SST9801
John J. Pagan	Elite Medical Research, Inc	DAP SST9801
William M. Reiter, M.D.	Community Hospital of Anaconda	DAP SST9801
	Protocol DAP-BAC9803	
Jordan B. Glaser, M.D.	Staten Island University Hospital	DAP-BAC9803
Monroe Karetzky, M.D.	Newark Beth Israel Medical Center	DAP-BAC9803
John W. King, M.D.	Louisiana State University Medical Center	DAP-BAC9803
Wickliffe Many, Jr., M.D.	University of Alabama School of Medicine	DAP-BAC9803
William M. Reiter, M.D. FACP	Community Hospital of Anaconda	DAP-BAC9803
Jan H. Westerman	Walker Baptist Medical Center	DAP-BAC9803
	Protocol DAP-RRC9804	
Robert S. Jones, DO	Berks Infectious Disease Services	DAP-RRC9804
John J. Pagan, M.D.	Elite Medical Research, Inc	DAP-RRC9804

4/19/99 Cubist — Letter authorizing FDA to incorporate by reference information submitted in Cubist IND 57,693 in its consideration of treatment IND 56,589 submitted by Carlos Subauste

5/17/99 IND 007 — Information Update: Addition of Investigators

	Protocol DAP-SST9801	
Ian M. Baird, MD	Grant / Riverside Methodist Hospitals	DAP SST9801
Dr. R. Decker	Mercy Hospital	DAP SST9801
Eliot Frank. M.D.	Jersey Shore Medical Center	DAP SST9801
Jordan B. Glaser, M.D.	Staten Island University Hospital	DAP SST9801
James Leggett, M.D.	Providence Health System	DAP SST9801
David J. McClain, M.D.	Mission/St. Joseph Health System	DAP SST9801
William M. Reiter, M.D. FACP	Community Hospital of Anaconda	DAP SST9801
R. Scott Stienecker, M.D.	Lima Memorial Hospital	DAP SST9801
	Protocol DAP-BAC9803	
Richard W. Carlson, M.D.	Maricopa Integrated Health Systems	DAP-BAC9803
Jordan B. Glaser, M.D.	Staten Island University Hospital	DAP-BAC9803
Monroe Karetzky, M.D.	Newark Beth Israel Medical Center	DAP-BAC9803
Arthur A. Mauceri, M.D.	North Florida Regional Medical Center	DAP-BAC9803
Wickliffe Many, Jr., M.D.	University of Alabama School of Medicine	DAP-BAC9803
David J. McClain, M.D.	Mission/St. Joseph Health System	DAP-BAC9803
William M. Reiter, M.D. FACP	Community Hospital of Anaconda	DAP-BAC9803

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Nina Singh, M.D.	Veteran Affairs Medical Center	DAP-BAC9803
R. Scott Stienecker, M.D.	Lima Memorial Hospital	DAP-BAC9803
Julio A. Remirez, M.D.	University of Louisville	DAP-BAC9803
	Protocol DAP-RRC9804	
Dr. R. Decker	Mercy Hospital	DAP-RRC9804
Eliot Frank. M.D.	Jersey Shore Medical Center	DAP-RRC9804
Jordan B. Glaser, M.D.	Staten Island University Hospital	DAP-RRC9804
James Leggett, M.D.	Providence Health System	DAP-RRC9804
Arthur A. Mauceri, M.D.	North Florida Regional Medical Center	DAP-RRC9804
Nina Singh, M.D.	Veteran Affairs Medical Center	DAP-RRC9804
R. Scott Stienecker, M.D.	Lima Memorial Hospital	DAP-RRC9804
David J. McClain, M.D.	Mission/St. Joseph Health System	DAP-RRC9804
John W. King, M.D.	Louisiana State University Medical Center	DAP-RRC9804

5/20/99 Cubist

Letter to Jose Cintron announcing new European protocol, SST9901, and summarizing differences between SST9901 and SST9801, enclosing:

- SST9901 (without signature page) for review

5/24/99 FDA

Fax to Judy Newberne from Jose Cintron attaching:

- Minutes of the 12/2/98 Pre-IND meeting

6/7/99 IND 008

New Protocol Submission:

- European Protocol DAP SST9901
- List of obligations being transferred to CRO, Kendle International

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6/17/99 IND 009

Information Amendment

- Revised Proposal for Safety/Tolerability Interim Assessment of Daptomycin at 6mg/kg Q24h (conduct safety assessment on the combined data from studies DAP-BAC9803 and DAP RRC9804)

6/28/99 IND 010

Information Update: Addition of Investigators

	Protocol DAP-SST9801	
Barbara Atkinson, DO	Ft. Worth, TX	DAP SST9801
Mary Birmingham, Pharm. D.	Buffalo, NY	DAP SST9801
Paul Eder, M.D.	Baltimore, MD	DAP SST9801
Richard Fetchik, M.D.	San Antonio, TX	DAP SST9801
Susan Galandiuk, M.D.	Louisville, KY	DAP SST9801
Stephen Green	Newport News, VA	DAP SST9801
William Harley, M.D.	Charlotte, NC	DAP SST9801
Stephen Kagan, M.D.	Atlanta, GA	DAP SST9801
Adolf Karchmer, M.D.	Boston, MA	DAP SST9801
James Leggett, M.D.	Portland, OR	DAP SST9801
Dennis Mikolich, M.D.	Cranston, RI	DAP SST9801
Joseph Plouffe, M.D.	Columbus, OH	DAP SST9801
William Reiter, M.D.,FACP	Anaconda, MT	DAP SST9801
Leon Smith, M.D.	Newark, NJ	DAP SST9801
	Protocol DAP-BAC9803	
Barbara Atkinson, DO	Ft. Worth, TX	DAP-BAC9803

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Paul Eder, M.D.	Baltimore, MD	DAP-BAC9803
Richard Fetchik, M.D.	San Antonio, TX	DAP-BAC9803
William Harley, M.D.	Charlotte, NC	DAP-BAC9803
Kuo-Liang Huang, M.D.	Colton, CA	DAP-BAC9803
Donald Levine, M.D.	Detroit, MI	DAP-BAC9803
Joseph Plouffe, M.D.	Columbus, OH	DAP-BAC9803
Julio Ramirez, M.D.	Louisville KY	DAP-BAC9803
Julio Ramirez, M.D.	Louisville KY	DAP-BAC9803
William Reiter, M.D.,FACP	Anaconda, MT	DAP-BAC9803
David Snydman, M.D.	Boston, MA	DAP-BAC9803
Albert Yellin, M.D.	Los Angeles, CA	DAP-BAC9803
	Protocol DAP-RRC9804	
Barbara Atkinson, DO	Ft. Worth, TX	DAP-RRC9804
John Carroll, M.D.	Phoenix, AZ	DAP-RRC9804
Paul Eder, M.D.	Baltimore, MD	DAP-RRC9804
Richard Fetchik, M.D.	San Antonio, TX	DAP-RRC9804
Adolf Karchmer, M.D.	Boston, MA	DAP-RRC9804
Kuo-Liang Huang, M.D.	Colton, CA	DAP-RRC9804
James Leggett, M.D.	Portland, OR	DAP-RRC9804
Joseph Plouffe, M.D.	Columbus, OH	DAP-RRC9804
Nina Singh, M.D.	Pittsburgh, PA	DAP-RRC9804
David Snydman, M.D.	Boston, MA	DAP-RRC9804
Albert Yellin, M.D.	Los Angeles, CA	DAP-RRC9804

7/02/99 **Cubist**	Notification of fatal adverse event (6/24/99) BAC9803 by fax to Dr. Chikami from Andy Knapp to be followed up with a Safety Report submission.
7/07/99 **Kendle**	Fax from Jenny Seaber to Judy Newberne attaching: • MCA confirmation of valid notification and statement that the 35 day assessment period commenced on 7/5/99
7/12/99 **Cubist**	Fax to Dr. Chikami at the FDA by Judy Newberne containing letter with Cubist's request for proposed brand names
7/12/99 **IND 011**	General Correspondence Submission: • Request for brand names Cidecin, Cubicin, Cydopril and Zencid
7/15/99 **IND 012**	Safety Report Submission: • Initial Safety Report Protocol BAC9803 (SAE 6/24/99)
7/22/99 **IND 013**	Protocol Amendment Submission: • Protocol Amendment 1 to BAC9803 (modifying inclusion/exclusion)
7/30/99 **FDA**	Fax from Jose Cintron attaching: • Statistical Comments, Dr. Brittain, Protocol SST9901
8/4/99 **IND 014**	Safety Report Submission: • Initial Safety Report: Protocol RRC9804 (SAE 7/8/99)

8/05/99 Cubist	Fax to Steve Trostle requesting clarification of a portion of Dr. Brittain's 2/99 statistical comments on SST9801, BAC9803, and RRC9804.
8/13/99 IND 015	General Correspondence Submission: • Response to FDA Statistical Comments for Protocols SST9801 and BAC9803
8/13/99 IND 016	Letter stating discovery of errors and changes in data interpretation of Lilly's original study reports; errors to be addressed and amended study reports to be submitted. General Correspondence Submission: • Daptomycin Manuscript Review Paper: "A Novel Agent for Gram-positive Infections" in *Expert Opinion on Investigational Drugs*, August 1999
8/20/99 IND 017	Protocol Amendment Submission, re: IND 008 - SST9901: • Amendment 1, dated 6/2/99, Israel only – to permit cloxacillin as choice for semi-synthetic penicillin • Amendment 2, dated 7/20/99, Spain only – to permit cloxacillin as only choice for semi-synthetic penicillin since flucloxacillin and oxacillin not marketed in Spain.
9/23/99 IND 018	Information Update: Change from Claudio Carini, M.D. to Michael DeBruin, M.D. as the person responsible for monitoring the conduct, progress and safety of clinical investigations at Cubist
9/23/99 IND 019	Addition of Investigators and update to Investigator Information, Protocol DAP SST9801, DAP BAC9803 and DAP RRC9804

	Protocol DAP-SST9801	
William Cheadle, M.D.	Louisville, KY	DAP SST9801
Stephen Green, M.D.	Newport News, VA	DAP SST9801
Jay Kislak, M.D.	New York, NY	DAP SST9801
Dennis Maki	Madison, WI	DAP SST9801
William Reiter, M.D.,FACP	Anaconda, MT	DAP SST9801
Leon Smith	Newark, NJ	DAP SST9801
	Protocol DAP-BAC9803	
Barbara Atkinson, DO	Ft. Worth, TX	DAP-BAC9803
Jack Bernstein, M.D.	Dayton, OH	DAP-BAC9803
Jay Kislak, M.D.	New York, NY	DAP-BAC9803
Amy Beth Kressel, M.D.	Cincinnati, OH	DAP-BAC9803
Dennis Maki	Madison, WI	DAP-BAC9803
George Pankey, M.D.	New Orleans, LA	DAP-BAC9803
William Reiter, M.D.,FACP	Anaconda, MT	DAP-BAC9803
Randi Silibovsky, M.D.	Philadelphia, PA	DAP-BAC9803
Jan Westerman, M.D.	Jasper, AL	DAP-BAC9803

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Protocol DAP-RRC9804		
Jay Kislak, M.D.	New York, NY	DAP-RRC9804
Amy Beth Kressel, M.D.	Cincinnati, OH	DAP-RRC9804
Donald Levine, M.D.	Detroit, MI	DAP-RRC9804
Dennis Maki	Madison, WI	DAP-RRC9804
George Pankey, M.D.	New Orleans, LA	DAP-RRC9804
Julio Ramirez, M.D.	Louisville, KY	DAP-RRC9804
William Reiter, M.D.,FACP	Anaconda, MT	DAP-RRC9804
Randi Silibovsky, M.D.	Philadelphia, PA	DAP-RRC9804

9/23/99 IND 020

Information Update Submission:

- Summary of Daptomycin Interim Safety Analysis with data package

9/28/99 FDA

Fax from Jose Cintron attaching:

- Statistical comments, Dr. Brittain, on Cubist's statistical response (IND 015) submitted 8/13/99

10/25/99 IND 021

Protocol Amendment Submission SST9901:

- Amendment 3 SST9901 (Investigator blinding, comparator to "Selected Semi-Synthetic Penicillin"). Also notification of S. Africa as site.

11/22/99 IND 022

Information Update: Addition of Investigators and update Investigator Information, Protocols DAP SST9801, DAP BAC9803 and DAP RRC9804

Protocol DAP-SST9801		
John R. Burge, M.D.	Danville, VA	DAP SST9801
Myles E. Gombert, M.D.	Port Washington, NY	DAP SST9801
Fred Grynberg, M.D.	Miami Beach, FL	DAP SST9801
Christopher Lucasti, DO	Cape May Court House, NJ Somers Point, NJ	DAP SST9801
Arthur Mauceri, M.D.	Gainesville, FL	DAP SST9801
Dennis Mikolich, M.D.	Cranston, RI	DAP SST9801
Ronald Nahass, M.D., FACP, FIDSA	Somerville, NJ	DAP SST9801
Russell Postier, M.D.	Oklahoma City, OK	DAP SST9801
Richard Snyder, M.D.	Allentown, PA	DAP SST9801
Joseph Solomkin, M.D.	Cincinnati, OH	DAP SST9801
Kenneth Rolston, M.D.	Houston, TX	DAP SST9801
R. Scott Stienecker, M.D.	Cincinnati, OH	DAP SST9801
Protocol DAP-BAC9803		
Bradley Britigan, M.D.	Iowa City, IA	DAP-BAC9803
John R. Burge, M.D.	Danville, VA	DAP-BAC9803
Myles E. Gombert, M.D.	Port Washington, NY	DAP-BAC9803
Fred Grynberg, M.D.	Miami Beach, FL	DAP-BAC9803
Joseph John, Jr. M.D.	New Brunswick, NJ	DAP-BAC9803
Harvey Kantor, M.D.	Odessa. TX	DAP-BAC9803
Arthur Mauceri, M.D.	Gainesville, FL	DAP-BAC9803
Ronald Nahass, M.D., FACP, FIDSA	Somerville, NJ	DAP-BAC9803
Joseph Plouffe, M.D.	Columbus, OH	DAP-BAC9803
Julio Ramirez, M.D.	Louisville, KY	DAP-BAC9803

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Graham C. Scott, M.D.	Charleston, SC	DAP-BAC9803
David Smith, Maj., USAF, MC	Lackland AFB, TX	DAP-BAC9803
David Snydman, M.D.	Boston, MA	DAP-BAC9803
Ronald A. Squires, M.D.	Oklahoma City, OK	DAP-BAC9803
R. Scott Stienecker, M.D.	Cincinnati, OH	DAP-BAC9803
Zelalem Temesgen, M.D.	Rochester, MN	DAP-BAC9803
	Protocol DAP-RRC9804	
Bradley Britigan, M.D.	Iowa City, IA	DAP-RRC9804
John R. Burge, M.D.	Danville, VA	DAP-RRC9804
Fred Grynberg, M.D.	Miami Beach, FL	DAP-RRC9804
Harvey Kantor, M.D.	Odessa. TX	DAP-RRC9804
Carlos Lopez, M.D.	Atlanta, GA	DAP-RRC9804
Christopher Lucasti, DO	Cape May Court House, NJ, Somers Point, NJ	DAP-RRC9804
Arthur Mauceri, M.D.	Gainesville, FL	DAP-RRC9804
Ronald Nahass, M.D., FACP, FIDSA	Somerville, NJ	DAP-RRC9804
Graham C. Scott, M.D.	Charleston, SC	DAP-RRC9804
David Smith, Maj., USAF, MC	Lackland AFB, TX	DAP-RRC9804
Richard Snyder, M.D.	Allentown, PA	DAP-RRC9804
David Snydman, M.D.	Boston, MA	DAP-RRC9804
Ronald A. Squires, M.D.	Oklahoma City, OK	DAP-RRC9804
Jan H. Westerman, M.D.	Jasper, AL	DAP-RRC9804

01/13/00
IND 023

Safety Report Submission:
Initial Safety Report; Protocol DAP-SST9801 (SAE 12/28/99)

1/21/00
IND 024

Protocol Amendment Submission SST9901:

- Amendment 4 SST9901, dated 12/20/99, South Africa only (inclusion/exclusion)

01/24/00
IND 025

Addition of Investigators and update to Investigator Information, Protocol DAP SST9801, DAP BAC9803 and DAP RRC9804 and Contract Research Organization, IBAH, Inc

	Protocol DAP-SST9801	
Ian Baird	Columbus, OH	DAP-SST9801
Sylvia Firary	LaCrosse, WI	DAP-SST9801
Fred Grynberg, M.D.	Miami, FL	DAP-SST9801
Mark Harrison, M.D.	Berrien Center, MI	DAP-SST9801
Dr. Kinasewitz, M.D.	Oklahoma City, OK	DAP-SST9801
Peter Krumpe, M.D.	Reno, NY	DAP-SST9801
Dennis Mikolich, M.D.	Cranston, RI	DAP-SST9801
Larry Rumans	Topeka, KS	DAP-SST9801
Roger Schmid, M.D.	Sun City, AZ	DAP-SST9801
Richard Snyder, M.D.	Allentown, PA	DAP-SST9801
David Talan/Gregory Moran	Sylmar, CA	DAP-SST9801
Ravi Vemuri, M.D.	Desmoines, IA	DAP-SST9801
	Protocol DAP-BAC9803	
Scott Bonvallet	Bellevue, WA	DAP-BAC9803
Robert Cantey, M.D.	Charleston, SC	DAP-BAC9803

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Diana Dark, M.D.	Kansas City, MO	DAP-BAC9803
Robert Duncan, M.D.	Burlington, MA	DAP-BAC9803
Sylvia Firary	LaCrosse, WI	DAP-BAC9803
Fred Grynberg, M.D.	Miami, FL	DAP-BAC9803
Mark Harrison, M.D.	Berrien Center, MI	DAP-BAC9803
Robert Kearl, M.D.	Phoenix, AZ	DAP-BAC9803
Dr. Kinasewitz, M.D.	Oklahoma City, OK	DAP-BAC9803
Peter Krumpe, M.D.	Reno, NY	DAP-BAC9803
Carlos Marchini, M.D.	Grants Pass, OR	DAP-BAC9803
Larry Rumans	Topeka, KS	DAP-BAC9803
Roger Schmid, M.D.	Sun City, AZ	DAP-BAC9803
	Protocol DAP-RRC9804	
Scott Bonvallet	Bellevue, WA	DAP-RRC9804
Robert Duncan, M.D.	Burlington, MA	DAP-RRC9804
Sylvia Firary	LaCrosse, WI	DAP-RRC9804
Fred Grynberg, M.D.	Miami, FL	DAP-RRC9804
Dr. Kinasewitz, M.D.	Oklahoma City, OK	DAP-RRC9804
Peter Krumpe, M.D.	Reno, NY	DAP-RRC9804
Carlos Marchini, M.D.	Grants Pass, OR	DAP-RRC9804
Larry Rumans	Topeka, KS	DAP-RRC9804
Richard Snyder, M.D.	Allentown, PA	DAP-RRC9804

02/18/00 IND 026

Response to FDA Statistical Comments, Reference is made to Agency's 2/19/99 letter outlining statistical concerns relating to clinical protocols DAP SST9801

3/01/00 IND 027

Request to Agency for End of Phase 2 Meeting

03/09/00 IND 028

Addition of Investigators and Change in Investigator Information, Protocols DAP SST9801, DAP BAC9803, DAP RRC9804 and DAP SST9901

	Protocol DAP-SST9801	
Robert Armour Force, M.D.	Boston, MA	DAP SST9801
Robert Muder, M.D.	Pittsburgh, PA	DAP SST9801
William Reiter, M.D., F.A.C.P.	Anaconda, MT	DAP SST9801
Robert R. Tight, M.D.	Fargo, ND	DAP SST9801
	Protocol DAP-BAC9803	
Robert Armour Force, MD	Boston, MA	DAP-BAC9803
William Reiter, M.D., F.A.C.P.	Anaconda, MT	DAP-BAC9803
David Snydman, M.D.	Boston, MA	DAP-BAC9803
Dennis L. Stevens, M.D., Ph.D.	Boise, ID	DAP-BAC9803
Robert R. Tight, M.D.	Fargo, ND	DAP-BAC9803
	Protocol DAP-RRC9804	
William Reiter, M.D., F.A.C.P.	Anaconda, MT	DAP-RRC9804
David Snydman, M.D.	Boston, MA	DAP-RRC9804
Robert R. Tight, M.D.	Fargo, ND	DAP-RRC9804
	Protocol DAP-SST9901	
	Belgium	
Prof. Dr. H. Van Hee	Antwerpen, Belgium	DAP-SST9901
	Germany	
Prof. Dr. Med. Hermann R. Ochs	Soest, Germany	DAP-SST9901
Dr. Med. Klaus-Peter Reetz	Hofheim, Germany	DAP-SST9901

	Israel	
Prof. Michael R. Dan	Holon, Israel	DAP-SST9901
Dr. David Hassin	Hadera, Israel	DAP-SST9901
	South Africa	
Dr. Johan Geyser	Conera, South Africa	DAP-SST9901

3/14/00 IND 029	Phase 1 Protocol DAP 00 01: Renal Insufficiency, End Stage Renal Disease and Healthy Volunteers
03/21/00 IND 030	Confirmation letter confirming End of Phase 2 and CMC Meetings to be held on May 12, 2000 at 10:00 a.m. for CMC and May 16, 2000 at 10:00 a.m. for End of Phase 2 data
4/10/00 IND 031	Cubist first Annual Report for IND 57,693
04/11/00 IND 032	Final report Bridging Toxicology Report 44 "A Comparison Intravenous Toxicity Study of Two Manufactured Lots of Daptomycin in Rats"
4/17/00 IND 033	End of Phase 2 Meeting Package for meeting on CMC, May 12, 2000 and End of Phase 2, May 16, 2000
04/19/00 IND 034	Safety Report Submission: Initial Safety Report; Protocol DAP-BAC9803 (SAE 03/10/00)
5/03/00 IND 035	Safety Report Submission: Initial Safety Report; Protocol DAP-BAC9803 (SAE 04/14/00) and DAP RRC9804 (SAE 04/01/00)
05/09/00 IND 036	Addition of Investigators: Protocol 00-01: Renal Insufficiency, End Stage Renal Disease and Healthy Volunteers and Investigator Information
5/10/00 IND 037	Postponement of End of Phase 2/Clinical Meeting: May 16, 2000 to discuss the Phase 3 cUTI Study
05/16/00 IND 038	Addition of Investigators and Change in Investigator Information Protocols DAP-SST9801, DAP-BAC9803 and DAP-RRC9804

Protocol DAP-SST9801

Steven Daugherty, MD	Springfield, MO	DAP SST9801
Thomas Deskin, MD	Kansas City, MO	DAP SST9801
Robert Armour Forse, MD, Ph.D	Boston, MA	DAP SST9801
Richard Gonzalez, MD	Mobile, AL	DAP SST9801

Robert Jones, DO	West Reading, PA	DAP SST9801
Frances Haas, DO	Tulsa, OK	DAP SST9801
Gary Kinasewitz, MD	Oklahoma City, OK	DAP SST9801
Nelson Madrilejo, MD	Bakersfield, CA	DAP SST9801
David Minion, MD	Lexington, KY	DAP SST9801
Miguel Mogyoros, MD	Denver, CO	DAP SST9801
Robert Muder, MD	Pittsburgh, PA	DAP SST9801
Ronald Nahass, MD, FACP, FIDSA	Somerville, NJ	DAP SST9801
Michael Steven Oleksyk, MD	Pensacola, FL	DAP SST9801
Richard Prokesch, MD	Riverdale, GA	DAP SST9801
William Reiter, MD	Anaconda, MT	DAP SST9801
Larry Rumans, MD	Topeka, KS	DAP SST9801
Mark Rumbak, MD	Tampa, FL	DAP SST9801
Prescilla Sioson, MD	Jackson, TN	DAP SST9801
R. Scott Steinecker, MD	Lima, OH	DAP SST9801
Darrell Stuart, MD	Toledo, OH	DAP SST9801
David Talan, MD	Sylmar, CA	DAP SST9801
Ben Thompson, MD	Lake Charles, LA	DAP SST9801
Robert Tight, MD	Fargo, ND	DAP SST9801
Lisa Vesch, MD	Des Moines, IA	DAP SST9801
John Weigelt, DVM, MD	Milwaukee, WI	DAP SST9801
Rodney Wishnow, MD	Long Beach, CA	DAP SST9801
	Protocol DAP-BAC9803	
Diana Dark, MD	Kansas City, MO	DAP-BAC9803
Robert Duncan, MD	Burlington, MA	DAP-BAC9803
Robert Armour Forse, MD, Ph.D.	Boston, MA	DAP-BAC9803
Carlos Lopez, MD	Atlanta, GA	DAP-BAC9803
Gary Kinasewitz, MD	Oklahoma City, OK	DAP-BAC9803
Ronald Nahass, MD, FACP, FIDSA	Somerville, NJ	DAP-BAC9803
Richard Prokesch, MD	Riverdale, GA	DAP-BAC9803
William Reiter, MD, FACP	Anaconda, MT	DAP-BAC9803
Larry Rumans, MD	Topeka, KS	DAP-BAC9803
Mark Rumbak, MD	Tampa, FL	DAP-BAC9803
David Snydman, MD	Boston, MA	DAP-BAC9803
R. Scott Steinecker, MD	Lima, OH	DAP-BAC9803
Dennis Stevens, MD, Ph.D.	Boise, ID	DAP-BAC9803
Robert Tight, MD	Fargo, ND	DAP-BAC9803
	Protocol DAP-RRC9804	
Richard Gonzalez, MD	Mobile, AL	DAP-RRC9804
Robert Jones, DO	West Reading, PA	DAP-RRC9804
Gary Kinasewitz, MD	Oklahoma City, OK	DAP-RRC9804
Carlos Lopez, MD	Atlanta, GA	DAP-RRC9804
Ronald Nahass, MD, FACP, FIDSA	Somerville, NJ	DAP-RRC9804
Richard Prokesch, MD	Riverdale, GA	DAP-RRC9804
William Reiter, MD, FACP	Anaconda, MT	DAP-RRC9804
Larry Rumans, MD	Topeka, KS	DAP-RRC9804
David Snydman, MD	Boston, MA	DAP-RRC9804

05/19/00
IND 039

Protocol Amendment No 2 to Study DAP-BAC9803 Protocol Amendment No 2 to Study DAP-BAC9803 "A multicenter, open-label, randomized study to compare the safety and efficacy of IV Daptomycin with that of Vancomycin or a semi-synthetic penicillin in the treatment of bacteremic infections due to gram-positive bacteria."

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05/19/00 IND 040	Protocol Amendment No 1 to Study DAP-RRC9804 Protocol Amendment No 1 to Study DAP-RRC9804 " A multicenter, open-label, non-comparative study to assess the safety and efficacy of IV Daptomycin in the treatment of hospitalized subjects with infections due to gram positive bacteria that are resistant to vancomycin or who are otherwise refractory to, or contraindicated for a currently available therapy."
05/19/00 IND 041	Request for an End of Phase 2 Meeting
05/31/00 IND 042	Addition of Investigators, Protocol DAP-SST9901, conducted in Europe, South Africa and Australia

Protocol DAP-SST9901

	France	
Dr. Oliver Bastien	Lyon, France	DAP SST9901
Pr. Jacques-Andre Bazex	Toulouse, France	DAP SST9901
Pr. J.M. Bonnetblanc	Limoges, France	DAP SST9901
Dr. Alain Bouvet	Caen, France	DAP SST9901
Pr. Frederic Cambazard	St. Etienne, France	DAP SST9901
Pr. Daniel Christmann	Strasbourg, France	DAP SST9901
Pr. Jean-Pierre Ducroix	Amiens, France	DAP SST9901
Dr. Jean Marie Estavoyer	Besancon, France	DAP SST9901
Dr Jacques Gaillat	Annecy, France	DAP SST9901
Dr. Loick Geffray	Lisieux, France	DAP SST9901
Dr. Bernard Habozit	Chambery, France	DAP SST9901
Prof. Pascal Joly	Rouen, France	DAP SST9901
Dr. Alain Lafeuilade	Toulon, France	DAP SST9901
Dr. Jamil Rahmani	Levallois-Perret, France	DAP SST9901
Jean-Paul Stahl	Grenoble, France	DAP SST9901
Pierre Veyssier	Compiegne, France	DAP SST9901
	United Kingdom	
Dr. Martin J. Wood	Birmingham, UK	DAP SST9901
	Austria	
Prof. Dr. med. Fritsch	Innsbruck, Austria	DAP SST9901
	Belgium	
Prof. Dr. H. Degreef	Leuven, Belgium	DAP SST9901
P. de Merlier, M.D.	Antwerpen, Belgium	DAP SST9901
	Australia	
Dr. William J. Hannan McBride	Cairns, Australia	DAP SST9901
Dr. David Craig Sowden	Nambour, Australia	DAP SST9901
	Germany	
Dr. med G. Baitsch	Bad Sackingen, Germany	DAP SST9901
Prof. Dr. med. Manfred Hagedorn	Darmstadt-Eberstadt, Germany	DAP SST9901
Dr. med. G. Hartleb	Kamen, Germany	DAP SST9901
Prof. Dr. med. Heidelore Hofmann	Munchen, Germany	DAP SST9901
PD Dr. med. Hans-Reinhardt Brodt	Frankfurt, Germany	DAP SST9901
Prof. Dr. Thomas Schwartz	Munster, Germany	DAP SST9901
Dr. med StraBburg	Berlin, Germany	DAP SST9901
	South Africa	
Dr. AK Atherstone	East London, S. Africa	DAP SST9901
Dr. Johan Geyser	Conera, S. Africa	DAP SST9901
Mr. F. Ghimenton	Pietermaritzburg, S. Africa	DAP SST9901
Mr. Balasundurum Govender	Chatsworth, Duban, S. Africa	DAP SST9901
Prof. J.E.J. Krige	Cape Town, S. Africa	DAP SST9901
Dr. P.A. Matthews	Middelburg, S. Africa	DAP SST9901
Dr. S. S. Pillay	Korsten, Port Elizabeth, S. Africa	DAP SST9901

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Dr. A Stettbacher	Cape Town, S. Africa	DAP SST9901
Dr. D. Theunissen	Wynberg, S Africa	DAP SST9901
Dr. F. Tun	Vergenoeg, Kimberley, S. Africa	DAP SST9901
Dr. L. Van Zyl	Worchester, S. Africa	DAP SST9901
Dr. D.J. Vermeulen	Somerset West, S. Africa	DAP SST9901
Prof. B.L. Warren	Parow, S. Africa	DAP SST9901

06/06/00 IND 043 — IND Initial Safety Report Follow-up Protocol DAP BAC9803

06/08/00 IND 044 — End of Phase 2 Meeting Package

06/08/00 IND 045 — May 12 CMC Meeting Minutes

06/16/00 IND 046 — Phase 1 Protocol DAP-00-02: A Randomized, double-blind, Multiple Dose, Pharmacokinetic and Safety Study of Ascending Dose of Daptomycin in Healthy Volunteers

06/19/00 IND 047 — Addition of Investigators, Protocols DAP SST9801 and DAP BAC9803

Protocol DAP-SST9801

Lynne Anderson, M.D.	Bay Pines, FL	DAP-SST9801
Glenn D. Bedsole, M.D.	Montgomery AL	DAP-SST9801
Brian J. Daley, M.D.	Knoxville, TN	DAP-SST9801
Robert W. DeConti, M.D.	Richmond, VA	DAP-SST9801
William Thomas Dickey, M.D.	Irving, TX	DAP-SST9801
Gerald R. Donowitz, M.D.	Charlottesville, VA	DAP-SST9801
Robert Eng, M.D.	E. Orange, NJ	DAP-SST9801
Marc Evan Fernandez, M.D.	Inverness, FL	DAP-SST9801
Byron E. Green, M.D.	Mobile, AL	DAP-SST9801
Shaun Healy, M.D.	Troy, MI	DAP-SST9801
Hoi Ho, M.D.	El Paso, TX	DAP-SST9801
Robert P. Holman, M.D.	Arlington, VA	DAP-SST9801
Lewis J. Kaplan, M.D.	Philadelphia, PA	DAP-SST9801
Peter Marsh, M.D./Lawrence Schwartz, M.D.	Tacoma, WA	DAP-SST9801
Thomas A. Moore, M.D.	Wichita, KS	DAP-SST9801
James H. North, Jr., M.D.	Fort Gordon, GA	DAP-SST9801
John J. Reddington, M.D	Denver, CO	DAP-SST9801
Roger B. Schechter, M.D.	Escondido, CA	DAP-SST9801
Robert Schwartz, M.D.	Fort Myers, FL	DAP-SST9801
Harold C. Standiford, M.D.	Baltimore, MD	DAP-SST9801
Peter S. Vrooman, Jr., M.D.	Winston-Salem, NC	DAP-SST9801

Protocol DAP-BAC9803

Richard P. Gonzalez, M.D.	Mobile, AL	DAP-BAC9803

06/22/00 IND 048 — Investigator's Brochure (Version 2)

06/29/00 IND 049 — Investigator Update (Dr. Maria Gutierrez) Phase 1 Protocol DAP-00-02: A Randomized, double-blind, Multiple Dose, Pharmacokinetic and Safety Study of Ascending Dose of Daptomycin in Healthy Volunteers

07/06/00 FDA — Fax from Agency to Cubist with minutes to teleconference held on May 9th, 2000

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07/07/00 Cubist	Pre IND Meeting request package sent to Canada Board of Pharmaceutical Assessment (HPB) to discuss submitting Canadian IND
07/14/00 CANADA	Fax from to Canada Board of Pharmaceutical Assessment (HPB) confirming Pre-IND meeting on 8/2/00
07/18/00 FDA	Fax from Jose Cintron (CSO) including comments from Dr. Moledina and Dr. Brittain for the CAP and cUTI protocols.
07/18/00 Cubist	Fax to Jose Cintron (CSO) with proposed CAP Study outline Fax notes that proposal will be officially submitted via FedEx as IND 050
07/19/00 IND 050	Submission of a Protocol Outline for a Phase II Study with Daptomycin in the Treatment of Community Acquired Pneumonia due to *Streptococcus Pneumoniae*
07/19/00 Cubist	Email from Erica Brittain to Jose Cintron at the FDA forwarded to Cubist with attached responses to Cubist 7/19/00 Memo
07/21/00 Cubist	Letter to Canada Bureau of Pharmaceutical Assessment (HPB) providing materials requested in the Bureau fax to Cubist on 7/14/00 for 8/2/00 Pre IND meeting
07/26/00 Cubist	Fax to Jose Cintron (CSO) IND 051 Community Acquired Pneumonia study Proposal
07/26/00 IND 051	Study Outline for Second Trial in Community Acquired Pneumonia
08/15/00 IND 052	Addition of Investigators and Change in Investigator Information, Protocols DAP SST9801, DAP-BAC9803, DAP-RRC9804 and DAP-SST9901

Protocol DAP-SST9801

Mary Birmingham, Pharm. D.	Buffalo, NY	DAP SST9801
Paul Eder, M.D.	Baltimore, MD	DAP SST9801
Stephen Hennigan, M.D.	Fayetteville, AR	DAP SST9801
Benjamin A. Lipsky, M.D.	Seattle, WA	DAP SST9801
Christopher Lacasti, M.D.	Somers Point, NJ	DAP SST9801
David McClain, M.D.	Asheville, NC	DAP SST9801
Thomas P. Nigra, M.D.	Washington, D.C.	DAP SST9801
Francis Pien, M.D.	Honolulu, HI	DAP SST9801
Russell Postier, M.D.	Oklahoma City, OK	DAP SST9801
Kenneth L. Quick, D.P.M.	Covington, LA	DAP SST9801
Eric Reines, M.D.	Alexandria, VA	DAP SST9801
William Reiter, M.D.,FACP	Anaconda, MT	DAP SST9801
Emil M. Skobeloff, M.D.	Upland, PA	DAP SST9801
Mark Alvin Strauss, M.D.	Little Rock, AR	DAP SST9801
Robert Tight, M.D.	Fargo, ND	DAP SST9801
Ravi Vemuri, M.D.	Des Moines, IA	DAP SST9801
Rodney Wishnow	Long Beach, CA	DAP SST9801
Leslie Zun, M.D.	Chicago, IL	DAP SST9801

Protocol DAP-BAC9803

David McClain, M.D.	Asheville, NC	DAP-BAC9803
William Reiter, M.D.	Anaconda, MT	DAP-BAC9803
David Snydman, M.D.	Boston, MA	DAP-BAC9803
Ronald Squires, M.D.	Charlotte, NC	DAP-BAC9803
Robert Tight, M.D.	Fargo, ND	DAP-BAC9803

Protocol DAP RRC9804

Christopher Lucasti, M.D.	Somers Point, NJ	DAP-RRC9804
David McClain, M.D.	Asheville, NC	DAP-RRC9804
Francis Pien, M.D.	Honolulu, HI	DAP-RRC9804

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William Reiter, M.D.	Anaconda, MT	DAP-RRC9804
David Snydman, M.D.	Boston, MA	DAP-RRC9804
Ronald Squires, M.D.	Charlotte, NC	DAP-RRC9804
Robert Tight, M.D.	Fargo, ND	DAP-RRC9804
	Protocol DAP SST9901	
	Australia	
Dr. Richard Lawrence	Kagarah, NSW	DAP SST9901
Dr. Jeffrey T.J. Rowland	Liverpool New	DAP SST9901
	Austria	
Pr. Dr. med. Paul Mischer	Wels	DAP SST9901
	Belgium	
Prof. Dr. H. Degreef	Leuven	DAP SST9901
	Czech Republic	
MU Dr. Jan Burger	Pribram	DAP SST9901
Dr. Vojtech Louda	Ceske Budejovice	DAP SST9901
Dr. Karel Nohejl	Prerov	DAP SST9901
Dr. Antonin Sevcik	Prague	DAP SST9901
	France	
Pr. Thierry May	Vandoeuvre	DAP SST9901
Dr. France Roblot	Poitiers	DAP SST9901
	Germany	
Prof. Dr. med Prof h.c. Bernd Rudiger Balda	Augsbury	DAP SST9901
Prof. Dr. med H. Bockhorn	Frankfurt	DAP SST9901
Prof. Dr. med Hans-Reinhardt Brodt	Frankfurt	DAP SST9901
Prof. Dr. med C. Eggers	Hamburg	DAP SST9901
Dr. med Helge Kotschau	Bad Oldesloe	DAP SST9901
	Hungary	
Dr. Janos Bende	Budapest	DAP SST9901
Dr. Elek Kisida	Budapest	DAP SST9901
Dr. Attila Olah	Vasvari	DAP SST9901
Dr. Endre Sziranyi	Budapest	DAP SST9901
	Israel	
Prof. Raul Raz	Afula	DAP SST9901
Prof. Ethan Rubinstein	Ramat-Gan	DAP SST9901
	South Africa	
Prof. J.H.R. Becker	Pretoria	DAP SST9901
Dr. H.J.C. Du Plessis	Thaba Tshwane	DAP SST9901
Prof. R.s. Du Toit	Bloemfontein	DAP SST9901
Prof. A.A. Haffejee	Durban	DAP SST9901
Dr. W. Rabie	Free State	DAP SST9901
Dr. J.H.R. Thomson	Durban	DAP SST9901
	Spain	
Dr. Manuel Marques	Malaga	DAP SST9901
Dr. Jordi de Otero	Barcelona	DAP SST9901
	Russia	
D.M. Prof. A. Shulutko	Moscow	DAP SST9901
	United Kingdom	
Dr. Edmund Ong	Newcastle upon Tyne	DAP SST9901
Dr. Martin J. Wiselka	Leicester	DAP SST9901
Dr. Martin Wood	Birmingham	DAP SST9901

08/23/00 IND 053	Amendment to DAP SST9801 and DAP SST9901
08/25/00 IND 054	IND Initial Safety Report- Protocol DAP 00-04 (SAE)
08/28/00 IND 055	July 12, 2000 End of Phase 2 Meeting Minutes submitted by Cubist to the Agency

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08/31/00 FDA	Fax from Jose Cintron (CSO) with Dr. Moledina's comments to fax sent to agency on July 26, 2000 ((Community Acquired Pneumonia Study Proposal
09/08/00 IND 056	Submission of Protocol DAP 00-05 ("*A Randomized, Double-Blind, Phase III, Comparative Study of Cidecin (Daptomycin) to Rocephin (Ceftriaxone) in the Treatment of Moderate to Severe Community-Acquired Acute Bacterial Pneumonia Due to S. Pneumonia*") and Amendment 1 to protocol DAP 00-05
09/14/00 IND 057	Change in Manufacturing Procedure for Daptomycin API and Manufacturer of Drug Product
09/20/00 CANADA	Letter from Bureau confirming receipt of IND Submission for CIDECIN in Canada
09/22/00 IND 058	Protocol DAP 00-03 and Amendment 1 to DAP 00-03 (cUTI Due to Gram-Positive Bacteria)
09/26/00 IND 059	IND Initial Safety Report Protocol SST-9901
09/26/00 Cubist	Fax to Jose Cintron (CSO) IND Initial Safety Report Protocol SST-9901 Letter
10/04/00 Cubist	Letter to Michael Cain, (CANADA) Responding to Bureau's request for clarification received September 26, 2000 of IND Submission in Canada
10/12/00 Cubist	Fax to Michel Bourdon, (CANADA), response to Bureau request for clarification received October 4, 2000 of IND Submission in Canada
10/12/00 Cubist	Letter to Michel Bourdon, (CANADA), response to Bureau request for clarification received October 4, 2000 of IND Submission in Canada
10/16/00 CANADA	Fax from Bureau requesting clarification of Protocol DAP 00-05
10/18/00 Cubist	Fax to David Venayak, (CANADA) Responding to request from teleconference call between Dr. Venayak and Bob McCormack
10/18/00 Cubist	Letter to David Venayak, (CANADA) Responding to request from teleconference call between Dr. Venayak and Bob McCormack
10/18/00 IND 060	Addition of Investigators and Change in Investigator Information Protocols DAP SST9801, DAP SST9901, DAP BAC9803, DAP RRC9804, and DAP 00-05

Protocol DAP-SST9801

Glen Bedsole, M.D.	Montgomery, AL	DAP SST9801
Joesph V. Boykin, Jr., M.D.	Richmond, VA	DAP SST9801
William T. Dickey, M.D.	Irving, TX	DAP SST9801
William T. Ellison, M.D.	Greer, SC	DAP SST9801
Raul E. Gaona, M.D.	San Antonio, TX	DAP SST9801
Tad E. Grenga, M.D.	Richmond, VA	DAP SST9801
Shaun Healy, M.D.	Troy, MI	DAP SST9801
Robert Holman, M.D.	Arlington, VA	DAP SST9801
Don L. James, M.D.	Rolla, MO	DAP SST9801
Nelson G. Madrilejo, M.D.	Bakersfield, CA	DAP SST9801
Miguel Mogyoros, M.D.	Denver, CO	DAP SST9801
Michael S. Oleksyk, M.D.	Pensacola, FL	DAP SST9801
Kenneth L. Quick, D.P.M.	Covington, LA	DAP SST9801
Jane Rohlf, M.D.	Trenton, NJ	DAP SST9801

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Richard S. Roth, M.D.	Savannah, GA	DAP SST9801
Robert Schwartz, M.D.	Fort Myers, FL	DAP SST9801
Harold C. Standiford, M.D.	Baltimore, MD	DAP SST9801
James Stem, M.D.	Hollywood, FL	DAP SST9801
J. Richard Taylor, M.D.	Miami, FL	DAP SST9801
Raymond E. Tidman, M.D.	Blue Ridge, GA	DAP SST9801
Lisa Veach, M.D.	Des Moines, IA	DAP SST9801
Jeffery M. Weinberg, M.D.	New York, NY	DAP SST9801
	Protocol DAP-BAC9803	
Raul E. Gaona, M.D.	San Antonio, TX	DAP-BAC9803
Donald R. Graham, M.D.	Springfield, IL	DAP-BAC9803
Chiu-Bin Hsiao, M.D.	Buffalo, NY	DAP-BAC9803
Carlos E. Lopex, M.D.	Atlanta, GA	DAP-BAC9803
Donald Poretz, M.D.	Falls Church, VA	DAP BAC9803
Samuel E. Wilson, M.D.	Orange, CA	DAP-BAC9803
	Protocol DAP RRC9804	
Carlos Lopex, M.D.	Atlanta, GA	DAP-RRC9804
Donald Poretz, M.D.	Falls Church, VA	DAP-RRC9804
	Protocol DAP SST9901	
	Australia	
Dr. Patrick Aldons	Chemside, QLD	DAP SST9901
Dr. Katherine R. Clezy	Randwick, NSW	DAP SST9901
Dr. William J.H. McBride	Cairns, QLD	DAP SST9901
Dr. Brent Richards	Southport, QLD	DAP SST9901
	Czech Republic	
Dr. Ivan Hunak	Zlin	DAP SST9901
Dr. Vojtech Louda	Ceske Budejovice	DAP SST9901
Dr. Jaroslav Pavlis	Kladno	DAP SST9901
	Germany	
Prof. Dr. med C. Eggers	Hamburg	DAP SST9901
	Israel	
Dr. Ruth Kitzes Cohen	Haifa	DAP SST9901
Dr. Ruth Lang	Kefar Sava	DAP SST9901
Dr. Silvio Daniel Pitlik	Petach Tikva	DAP SST9901
Prof. Francisc Schlaeffer	Beer Sheva	DAP SST9901
	The Netherlands	
Prof. Dr. H.A. Bruining	Rotterdam	DAP SST9901
	South Africa	
Prof. J.E. J. Krige	Cape Town	DAP SST9901
Mr. U.K. Naidoo	Durban	DAP SST9901
	Spain	
Dr. Santiago Martinez Ratero	Madrid	DAP SST9901
Dr. Miquel Sanchez	Barcelona	DAP SST9901
Dr. Jesus Sanz	Madrid	DAP SST9901
	United Kingdom	
Dr. P. Jennings	York	DAP SST9901
	DAP-00 05	
	Canada	
Dr. Noel Lampron	Ste. Foy, QB	DAP 00 05
Stephan J. Landis, M.D.	Hamilton, ON	DAP 00 05
	United States	
Randy Dotson, M.D.	Mobile, AL	DAP 00 05

10/25/00 CANADA	Letter from Bureau approving Cubist IND Submission for CIDECIN
10/25/00 Cubist	Fax to Michael Cain, (CANADA) with the names of the three Principal Investigators in Canada
11/14/00 IND 061	Protocol DAP VE-00-07 (Suspended Vancomycin Resistant Enterococcal Infections.

11/17/00 IND 062 — Protocol DAP-00-05, Amendment No. 2

11/21/00 IND 063 — Addition of Investigators and Change in Investigator Information Protocols DAP-SST9901 and DAP 00-05

	Protocol DAP SST9901	
	Australia	
Dr. Jeffrey T.J. Rowland	Chermside, QLD	DAP SST9901
	Germany	
Dr. med. Christiane Bayerl	Mannheim	DAP SST9901
Prof. Dr. med. C. Eggers	Hamburg	DAP SST9901
Prof. Dr. med. Roland Kaufmann	Frankfurt	DAP SST9901
	The Netherlands	
Dr. E.P. Prens	Vlissingen	DAP SST9901
	Slovak Republic	
Jozef Belacek, M.D.	Bratislava	DAP SST9901
Dr. Andrej Eperjesi	Kosice	DAP SST9901
Dr. Michal Hubka	Bratislava	DAP SST9901
Dr. Peter Molnar	Banska Bystrica	DAP SST9901
	Spain	
Dr. Francisco Alvarez	Barcelona	DAP SST9901
Dr. Victor Asensi	Oviedo	DAP SST9901
Dr. Manuel Marques	Malaga	DAP SST9901
Dr. Valentin Perez Gomez	Madrid	DAP SST9901
	DAP-00 05	
	Australia	
Dr. Paul Fogarty	Box Hill	DAP 00 05
Stephan J. Landis, M.D.	Hamilton, ON	DAP 00 05
	Croatia	
Prof. S. Schonwald, M.D.	Zagreb	DAP 00 05
	Hungary	
Zsuzsa Rott, M.D.	Matrahaza	DAP 00 05
	New Zealand	
Dr. Graham David Mills	Hamilton	DAP 00 05
	United States	
Michael Brown, M.D.	Pensocola, FL	DAP 00 05
Richard Carlson, M.D.	Phoenix, AZ	DAP 00 05
William J. Curley, M.D.	Las Vegas, NV	DAP 00 05
Peter Decpinigaitis, M.D.	Bronx, NY	DAP 00 05
Bruce Friedman, M.D.	Augusta, GA	DAP 00 05
Nelson Gantz	Harrisburg, PA	DAP 00 05
Paul Gennis, M.D.	Bronx, NY	DAP 00 05
Frances Haas, D.O.	Tulsa, OK	DAP 00 05
James Kruse, M.D.	Detroit, MI	DAP 00 05
Robert Larimer, M.D.	New Orleans, LA	DAP 00 05
Gary J. Richmond, M.D.	Fort Lauderdale, FL	DAP 00 05
Leonard Rosoff, M.D.	New Hyde Park, NY	DAP 00 05
Priscilla Sioson, M.D.	Jackson, TN	DAP 00 05
Austin B. Thompson, M.D.	Omaha, NE	DAP 00 05
Ignatius Thomas, M.D.	Slidell, LA	DAP 00 05
C. Kevin Watt, D.O.	Springfield, MO	DAP 00 05
Ronald B. Ziman, M.D.	Granada Hillis, CA	DAP 00 05

11/22/00 FDA — Fax from Agency with Meeting minutes for the End of Phase 2 meeting held on July 12, 2000

11/22/00 FDA — Letter from Agency (Division of Drug Marketing, Advertising, and Communications' (DDMAC)) on web and publication content

11/28/00 Cubist — Submission of Protocol DAP 00-05 and Amendment 2 to HPB

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12/01/00 CANADA	Fax from HPB regarding need for Cubist to submit an IND Submission Certificate
12/01/00 Cubist	Letter to DDMAC with Cubist acknowledging receipt of November 22, 2000 correspondence and Cubist response.
12/07/00 IND 064	Submission of Protocol DAP SST9901, Amendment No. 9
12/07/00 Cubist	Submission of Protocol DAP 00-05 and Amendment No. 9 (WordPerfect) Versions to Canadian HPB
12/11/00 CANADA	Letter from HPB acknowledging receipt of Protocol DAP 00-05 and Amendment 2
12/13/00 FDA	Fax from DDMAC acknowledging receipt and acceptance Cubist response on December 1, 2000.
12/13/00 FDA	Fax from Agency with comments by Dr. Moledina and Dr. Brittain on Protocol DAP 00-05, Amendment No. 2
12/15/00 Cubist	Fax and letter to Canadian HPB with response to questions raised during December 13, 2000 conference call regarding Amendment 9
12/18/00 IND 065	General Correspondence: Letter to Agency regarding clarification of DDMAC statement 11/22/00
12/18/00 CANADA	Fax from HPB requesting clarification of two questions with Protocol DAP 00-05 Amendment 2
12/21/00 Cubist	Letter and Fax to Agency requesting Teleconference and/or Meeting for additional clarification of DDMAC statement 11/22/00
12/21/00 CANADA	Letter and Fax to HPB with clarification to questions raised with Protocol DAP 00-05 Amendment 2 on 12/18/00
12/21/00 IND 066	Addition of Investigators and Change in Investigator Information Protocols DAP-SST9801, DAP 00-03 and DAP 00-05

	Protocol DAP SST9801	
Ian Baird, M.D.	Columbus, OH	DAP SST9801
Mary C. Birmingham, Pharm.D	Buffalo, NY	DAP SST9801
John Carroll, M.D.	Phoenix, AZ	DAP SST9801
Gary Decker, M.D.	Wilkes-Barre, PA	DAP SST9801
Richard Fetchik, M.D.	San Antonio, TX	DAP SST9801
Elliot Frank, M.D.	Neptune, NJ	DAP SST9801
Myles E. Gombert, M.D.	Port Washington, NY	DAP SST9801
Richard Gonzalez, M.D.	Mobile, AL	DAP SST9801
Gary T. Kinasewitz, M.D.	Oklahoma City, OK	DAP SST9801
Christopher Lucasti, D.O.	Somer Point, NJ	DAP SST9801
David J. McClain, M.D.	Asheville, NC	DAP SST9801
Francis Pien, M.D.	Honolulu, HI	DAP SST9801
Leon Smith, M.D.	Newark, NJ	DAP SST9801
R. Scott Stienecker, M.D.	Lima, OH	DAP SST9801
Rodney Wishnow, M. D.	Long Beach, CA	DAP SST9801
	Protocol DAP 00-03	
	Croatia	
Prof. S. Schonwald, M.D.	Zagreb, Croatia	DAP 00-03
	Hungary	
Laszlo Kisbenedek, M.D.	Budapest, Hungary	DAP 00-03

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	Protocol DAP 00-05	
	Czech Republic	
Pavel Reiterrer, M.D.	Usti n. Labem, Czech Republic	DAP 00-05
	United States	
Ashok Fulambarker, M.D.	North Chicago, IL	DAP 00 05
Donald R. Graham, M.D.	Springfield, IL	DAP 00 05
Jeffrey R. Rehm, M.D.	Silver Spring, M.D.	DAP 00 05
Robert Schwartz, M.D.	Fort Myers, FL	DAP 00 05
Steven Weiss, M.D.	Denver, CO	DAP 00 05

12/27/00 CANADA — Fax from HPB stating no objections to Protocol DAP 00-05 Amendment 2

01/30/01 IND 067 — Submission of Protocol DAP-00-05, Amendment No. 3

01/22/01 FDA — Fax from DDMAC to Cubist responding to December 21, 2000 letter requesting teleconference meeting

02/01/01 IND 068 — Addition of Investigators and Change in Investigator Information Protocols DAP-SST9801, DAP-SST9901, DAP-00-03 and DAP 00-05

	Protocol DAP SST9801	
Paul E. Bankey, M.D.	Worchester, MA	DAP SST9801
Jeffrey Jensen, D.P.M.	Denver, CO	DAP SST9801
	Protocol DAP SST9901	
	Hungary	
Elek Kisida, M.D.	Budapest	DAP SST9901
	Spain	
Dr. Jordi de Otero	Barcelona	DAP SST9901
	DAP 00-03	
	Croatia	
Prof. S. Schonwald, M.D.	Zagreb	DAP 00 03
	Hungary	
Laszlo Kisbenedek, M.D.	Budapest	DAP 00 03
	South Africa	
Dr. Karl Kassier	Bloemfontein	DAP 00 03
	DAP-00 05	
	Canada	
Doria Grimard, M.D.	Quebec	DAP 00 05
Charles Harley, M.D.	Edmonton, Alberta	DAP 00 05
John MacCarthy, M.D.	New Westminster, BC	DAP 00 05
	France	
Pr. Jean-Claude Meurice	Poitiers	DAP 00 05
	Iceland	
Dr. Mar Kristjansson	Reykjavik	DAP 00 05
	South Africa	
Dr. P. Matthews	Middelburg	DAP 00 05
	Slovak Republic	
Prof. Ondrej Balint	Bratislava	DAP 00 05
	United States	
J.R. Allison, III, M.D.	Columbia, SC	DAP 00 05
Pierce C. Alexander, M.D.	Knoxville, TN	DAP 00 05
Devendra N. Amin, M.D.	Clearwater, FL	DAP 00 05
Carlos A. Camargo, M.D.	Boston, MA	DAP 00 05
William Thomas Dickey, M.D.	Irving, TX	DAP 00 05
Toni L. Ferrario, M.D.	Buffalo, NY	DAP 00 05
Cesar B. Guerrero, M.D.	Manrovia, CA	DAP 00 05
Mark Harrison, M.D.	Berrien Springs, MI	DAP 00 05
Darell E. Heiselman, D.O.	Akron, OH	DAP 00 05
Mark T. Herbert, M.D.	Columbus, OH	DAP 00 05
Chiu-Fu Lee, M.D.	Bellflower, CA	DAP 00 05
Michael Natalino, M.D.	San Antonio, TX	DAP 00 05

	Michael Reilly, M.D.	Kansas City, MO	DAP 00 05
	James E. Turner, M.D.	Sacramento, CA	DAP 00 05
	Domenick J. Sorresso, M.D.	Hudson, FL	DAP 00 05

02/02/01 FDA	Fax from Agency to Cubist with attached Memo from Dr. Peters stating basis for preclinical toxicology/pharmacology conclusion on neurotoxicity
02/08/01 IND 069	Proposed Drug-drug Interaction Study to be submitted with the NDA
02/14/01 IND 070	Submission of Protocol DAP-00-08
03/08/01 IND 071	Submission of Protocol DAP-HEP-00-09 *A Comparison of the Pharmacokinetics of Cidecin (Daptomycin) in Subjects with Impaired Hepatic Function (Childs-Pugh B) and in Matched Healthy Volunteers*
03/08/01 IND 072	Submission of Protocol DAP-VE-00-07/Amendment No. 1 *"A Randomized, Double-Blind, Double-Dummy, Phase III, Comparative Study of Cidecin (Daptomycin) and Zyvox (Linezolid) in the Treatment of Hospitalized Adults with Suspected Vancomycin-Resistant Enterococcal Infections."*
03/22/01 Cubist	Letter to Prof. Garnett with Procedural Letter #1 Cubist Study DAP-HEP-00-09
03/23/01 IND 073	Submission of Cubist Request for Pediatric Deferral
03/29/01 IND 074	Submission of Cubist's second Annual Report
04/05/01 IND 075	Addition of Investigators, Protocol DAP-00-03 and DAP-00-05, conducted in Europe, Canada and The United States

	Protocol DAP-00-03	
	Czech Republic	
Pavla Toufarova, M.D.	Plzen, Czech Republic	DAP 00-03
	Germany	
Prof. Kurt Naber	Straubing, Germany	DAP 00-03
	Greece	
Prof. Harry Bassaris	Patras, Greece	DAP 00-03
Dr. Michael Lykourinas	Athens, Greece	DAP 00-03
	Protocol DAP-00-05	
	Canada	
Dr. Real Brossoit	Granby, Quebec	DAP 00-05
Dr. Ronald Damant	Edmonton, AB	DAP 00-05
Dr. Anil Dhar	Windsor, ON	DAP 00-05
Michel Gagnon, M.D.	St. Charles-Borromee, Quebec	DAP 00-05
Brian Kashin, M.D.	Brampton, ON	DAP 00-05
Ken Kasper, M.D.	Winnipeg, MN	DAP 00-05
Ted Rogovein, M.D.	Toronto, ON	DAP 00-05
Guy Tellier, M.D.	St. Jerome, QB	DAP 00-05
	Finland	
Dr. Tapio Jussila	Tampere, Finland	DAP 00-05
	Greece	
Dr. Alexandra Gerogianni	Athens, Greece	DAP 00-05
	Russia	
Prof. Y.B. Belousov	Moscow, Russia	DAP 00-05
	Poland	
Prof. Eugenia Czestochowska	Gdansk, Poland	DAP 00-05
	Spain	
Dr. Elpidio Calvo	Madrid, Spain	DAP 00-05
	The Netherlands	
Nico Cox, M.D.	Groesbeek, The	DAP 00-05

	Netherlands	
	United States	
Ian Baird, M.D.	Columbus, OH	DAP 00-05
Bruno Digiovine, M.D.	Detroit, MI	DAP 00-05
James Dudley Fitz, M.D.	Tacoma, WA	DAP 00-05
Ali El-Solh, M.D.	Buffalo, NY	DAP 00-05
Mitchell Gittelman, D.O.	Silver Spring, MD	DAP 00-05
Dean J. Kereiakes, M.D.	Cincinnati, OH	DAP 00-05
Kathleen Mullane, D.O.	Maywood, IL	DAP 00-05
Alex J. Pareigis, M.D.	Moline, IL	DAP 00-05
Annette C. Reboli, M.D.	Camden, NJ	DAP 00-05
Marc M. Seelagy, M.D.	Trenton, NJ	DAP 00-05
George Zlupko, M.D.	Altoona, PA	DAP 00-05

04/06/01 Cubist	Cubist Safety Plan for Protocol DAP-VRE-00-07 Version 1.1
04/09/01 FDA	Fax from Agency to Cubist with attached Memo recommendations on VRE protocols
04/12/01 FDA	Fax from Agency to Cubist with Clinical Pharmacology/ Biopharmaceutics Review of DAP VE 00 07
04/16/01 Cubist	Fax to Agency with requested list of ongoing and completed clinical studies with daptomycin
04/25/01 Cubist	Fax to Agency (Attn: Nasim Moledina, M.D.) responding to 4/25/01 request for information to use in the Anti-Infective Advisory Committee meeting 4/27/01
05/08/01 IND 076	Protocol DAP-VRE-00-07, Response to FDA Communication Dated April 9, 2001
05/10/01 IND 077	Official Request for Pre-NDA Meeting
05/14/01 IND 078	Submission of Protocol DAP-HEP-00-09: "*A Comparison of the Pharmakinetics of Cidecin™ (Daptomycin) in Subjects with Impaired Hepatic Function (Childs-Pugh B) and in Matched Healthy Volunteers*" and Amendment 1
05/25/01 IND 079	Addition of Investigators, Protocols DAP-SST-9801, DAP-00-03, DAP-00-05 and VRE-00-07

	DAP-SST-9801	
	South Africa	
Dr. P. Matthews	Middleburgh, S. Africa	DAP-SST-9801
Dr. F. Tun	Free State, S. Africa	DAP-SST-9801
Dr. D. Vermeulen	Somerset West, S. Africa	DAP-SST-9801
Prof. B. Warren	Parrow, S. Africa	DAP-SST-9801
Prof. J.E.J. Krige	Cape Town, S. Africa	DAP-SST-9801
	Study DAP-00-05	
	Australia	
Dr. William J. McBride[+]	Cairns, Australia	DAP-SST-9801
Dr. Martin Phillips[+]	Perth, Australia	DAP-SST-9801
Dr. Brent Richards[+]	Southport, Australia	DAP-SST-9801
	Belgium	
Dr. Frederique Jacobs[+]	Brussels, Belgium	DAP-SST-9801
Dr. Hans Jonnaert[+]	Wetteren, Belgium	DAP-SST-9801
Dr. Luc Vanmaele[+]	Knokke-Heist, Belgium	DAP-SST-9801
	Canada	
Dr. Sabayasachi Bose	Saskatoon, SK	DAP-SST-9801
	Croatia	
Dr. Slobodan Milutinovic	Zagreb, Croatia	DAP-SST-9801
	Czech Republic	
Vaclav Havlik, M.D.	Benesov, Czech Republic	DAP-SST-9801

Libor Kamenik, M.D.	Praha, Czech Republic	DAP-SST-9801
Bohumil Kralicek, M.D.	Jihlava, Czech Republic	DAP-SST-9801
Jana Krynska, M.D.	Zlin, Czech Republic	DAP-SST-9801
Milan Kucera, M.D.	Breclav, Czech Republic	DAP-SST-9801
Petr Prusa, M.D.	Kladno, Czech Republic	DAP-SST-9801
	Finland	
Dr. Jukka Lumio	Tampere, Finland	DAP-SST-9801
	France	
Pr. Jean-Claude Bertrand	Saint-Etienne, France	DAP-SST-9801
Pr. Francoise Bricaire	Paris, France	DAP-SST-9801
Pr. Pierre Carles	Toulouse, France	DAP-SST-9801
Dr. Pascal Chanez	Montpellier, France	DAP-SST-9801
Dr. Jean-Michel Coulaud	Montfermeil, France	DAP-SST-9801
Dr. Jean-Claude Ducreux	Roanne, France	DAP-SST-9801
Dr. Jean-Marc Pone	Etampes, France	DAP-SST-9801
Dr. Anne Prud'homme	Tarbes, France	DAP-SST-9801
Dr. Alain Tenaillon	Evry, France	DAP-SST-9801
Dr. Laurent Vives	Saint-Gaudens, France	DAP-SST-9801
	Greece	
Dr. Pandora Christaki	Thessaloniki, Greece	DAP-SST-9801
Dr. George Chrysos	Piraeus, Greece	DAP-SST-9801
Pf. Nikolaos Siafakas	Heraklion-Crete, Greece	DAP-SST-9801
	Hungary	
Geza Bozoky, M.D.	Kecskemet, Hungary	DAP-SST-9801
Agnes Devai, M.D.	Budapest, Hungary	DAP-SST-9801
Andras Koncz, M.D.	Debrecen, Hungary	DAP-SST-9801
Zsuzsa Mark, M.D.	Torobalint, Hungary	DAP-SST-9801
Judit Lukacs, M.D.	Budapest, Hungary	DAP-SST-9801
Szvetlana Palinkasi, M.D.	Szolnok, Hungary	DAP-SST-9801
Zsuzsanna Sztancsik, M.D.	Gyula, Hungary	DAP-SST-9801
	New Zealand	
Dr. Catherine Godfrey	S. Auckland, New Zealand	DAP-SST-9801
	Poland	
Dr. Janusz Balanda	Nowe Ogrody, Poland	DAP-SST-9801
Prof. Pawel Gorski	Kopcinskiego, Poland	DAP-SST-9801
Prof. Waldemar Halota	Bydgoszoz, Poland	DAP-SST-9801
Prof. Jozef Malolepszy	Wroclaw, Poland	DAP-SST-9801
Prof. Witold Mlynarczyk	Poznan, Poland	DAP-SST-9801
Dr. Iwona Witkiewicz	Sokolowskiego, Poland	DAP-SST-9801
Prof. Krzysztof Wrabec	Wroclaw, Poland	DAP-SST-9801
	Russia	
N.G. Alieva, M.D	Moscow, Russia	DAP-SST-9801
Dr. A. Chuchalin	Moscow, Russia	DAP-SST-9801
L.P. Katasonova, M.D.	Moscow, Russia	DAP-SST-9801
Dr. V. Marinin	Moscow, Russia	DAP-SST-9801
Dr. A. Sinopalnikov	Moscow, Russia	DAP-SST-9801
L.S. Stratchounski, M.D.	Smolensk, Russia	DAP-SST-9801
Dr. S. Yakolev	Moscow, Russia	DAP-SST-9801
	Slovak Republic	
Dr. Marta Hajkova	Bratislava, Slovak Republic	DAP-SST-9801
Dr. Mojmir Konecny	Trnava, Slovak Republic	DAP-SST-9801
Jan Plutinsky, M.D.	Nitra-Zobor, Slovak Republic	DAP-SST-9801
	Spain	
Dr. Jose Alegre	Barcelona, Spain	DAP-SST-9801
Dr. Jose Castillo	Sevilla, Spain	DAP-SST-9801
Dr. Joaquin Lamela	Orense, Spain	DAP-SST-9801
	The Netherlands	
Dr. Arjan Rudolphus	Rotterdam, The Netherlands	DAP-SST-9801
	United States	
Salah AL Andary, M.D.	Clearwater, FL	DAP-SST-9801

C. Lynn Anderson, M.D.	Bay Pines, FL	DAP-SST-9801
Steven M. Belknap, M.D.	Peoria, IL	DAP-SST-9801
Mark A. Bernat, M.D.	Rocky Mount, NC	DAP-SST-9801
Jack M. Bernstein, M.D.	Dayton, OH	DAP-SST-9801
Nausherwan K. Burki, M.D.	Lexington, KY	DAP-SST-9801
Joseph C. Campbell, M.D.	Omaha, NE	DAP-SST-9801
Andrew Chan, M.D.	Sacramento, CA	DAP-SST-9801
Patrick Chang, M.D.	Philadelphia, PA	DAP-SST-9801
Michael Collins, M.D.	Hoover, AL	DAP-SST-9801
Kurt G. Datz, D.O.	Bismarck, ND	DAP-SST-9801
Marcus J. DiLorenzo, M.D.	Ocala, FL	DAP-SST-9801
Charles M. Fogarty, M.D.	Spartanburg, SC	DAP-SST-9801
Emmel B. Golden, M.D.	Memphis, TN	DAP-SST-9801
Randall R. Hanson, M.D.	Des Moines, IA	DAP-SST-9801
Don L. James, D.O.	Rolla, MO	DAP-SST-9801
Robert J. Kaner, M.D.	New York, NY	DAP-SST-9801
Monroe Karetzky, M.D.	Newark, NJ	DAP-SST-9801
Richard B. Kohler, M.D.	Indianapolis, IN	DAP-SST-9801
Robert F. Lodato, M.D.	Houston, TX	DAP-SST-9801
Thomas Mathias, D.O.	Pinellas Park, FL	DAP-SST-9801
Janet E. McElhaney, M.D.	Norfolk, VA	DAP-SST-9801
William P. Moran, M.D.	Winston-Salem, NC	DAP-SST-9801
Dan Olson, M.D.	Toledo, OH	DAP-SST-9801
Lucy Palmer, M.D.	Stony Brook, NY	DAP-SST-9801
Wendell Phillips, D.O.	Phoenix, AZ	DAP-SST-9801
Mark Rumbak, M.D.	Tampa, FL	DAP-SST-9801
Scott Stienecker, M.D	Lima, OH	DAP-SST-9801
Raymond Tidman, M.D.	Blue Ridge, GA	DAP-SST-9801
Richard Winn, M.D	Temple, TX	DAP-SST-9801
Scott Yates, M.D.	The Colony, TX	DAP-SST-9801
Ken Yoneda, M.D.	Mather, CA	DAP-SST-9801
Leslie Zun, M.D.	Chicago, IL	DAP-SST-9801
	DAP-00-03	
	Croatia	
Dr. Slobodan Milutinovic	Zagreb, Croatia	DAP-00-03
	Czech Republic	
Dr. Katerina Bartonickova	Prague, Czech Republic	DAP-00-03
Dr. Frantisek Zatura	Olomouc, Czech Republic	DAP-00-03
	Hungary	
Dr. Lazlo Farkas	Pecs, Hungary	DAP-00-03
Dr. Endre Szule	Kistarcsa, Hungary	DAP-00-03
Dr. Denes Repassy	Budapest, Hungary	DAP-00-03
Dr. Ferenc Torzsok	Gyor, Hungaryui	DAP-00-03
	South Africa	
Dr. N. Christopher	Durban, S. Africa	DAP-00-03
Dr. L. Coetzee	Pretoria, S. Africa	DAP-00-03
Dr. A.M. Grizic	Durban, S. Africa	DAP-00-03
Dr. P.J. Harden	Johannesburg, S. Africa	DAP-00-03
Prof. J.E.J. Krige	Cape Town, S. Africa	DAP-00-03
Dr. I.P. Levinson	Peitermaritzburg, S. Africa	DAP-00-03
Dr. T.M. MacKenzie	Durban, S. Africa	DAP-00-03
Dr. A.C. Schmidt	Parow, S. Africa	DAP-00-03
Dr. D. Smart	Johannesburg, S. Africa	DAP-00-03
Prof. I.M. Viljoen	Bloemfontein, S. Africa	DAP-00-03
Dr. S. Voss	Pretoria, S. Africa	DAP-00-03
	VRE-00-07	
	United States	
Larry Bush, M.D.	Atlantis, FL	DAP-VRE-00-07
Philip Brachman, M.D.	Atlanta, GA	DAP-VRE-00-07
Robert S. Jones, M.D.	West Reading, PA	DAP-VRE-00-07
Roger Stienecker, M.D.	Lima, OH	DAP-VRE-00-07

06/07/01 IND 080	Submission of Toxicology Reports 45, 46, and 47
06/07/01 IND 081	Follow-up Serious Adverse Event Safety Report Protocol DAP-RRC9804, Subject 30403J-S
07/06/01 IND 082	Serious Adverse Event Safety Report Protocol DAP-SST9801, Subject 53164
07/09/01 CANADA	File No. 9427-C099-21C/Control 068232 Serious Adverse Event Safety Report Protocol DAP-SST9801, Subject 53164
07/24/01 IND 083	Submission of the July 23, 2001, minutes to the teleconference meeting between Cubist and the Agency to discuss the proposed drug-drug interaction study
07/24/01 IND 084	Submission of protocol DAP-CAP-08, Amendment No. 1
07/27/01 IND 085	Submission of the July 12, 2001, minutes to the teleconference meeting between Cubist and the Agency to discuss the clinical study requirements for VRE label claims for daptomycin
07/31/01 CUBIST	Internal Memo: Listing sites in South Africa participating in the DAP-00-08 study
07/31/01 CUBIST	Fax to Agency with revised version of teleconference meeting that took place on July 12, 2001 between Cubist and Agency
07/31/01 IND 086	Resubmission of the July 12, 2001, minutes to the teleconference meeting between Cubist and the Agency to discuss the clinical study requirements for VRE label claims for daptomycin
08/01/01 IND 087	Submission of Amendment No. 2, DAP-VRE-00-07, and DAP-VRE-01-04 "A *Randomized, Double-Blind, Double-Dummy, Phase III, Comparative Study of Cidecin (Daptomycin) and Zyvox™ (Linezolid) in the Treatment of Hospitalized Adults with Suspected Vancomycin-Resistant Enterococcal Infections* "
08/06/01 IND 088	Confirmation of Pre-NDA Meeting at the Agency on November 16, 2001
08/15/01 IND 089	Submission of updated Investigator's Brochure 3.0 (July 25, 2001)
08/28/01 Minutes of Teleconference	Minutes of the FDA Teleconference to discuss the VRE Program for Daptomycin. (Unofficial;minutes to be submitted with VRE Amendment)
08/28/01 IND 090	Submission of Protocol DAP-01-01: "*A double-Blind, Randomized, Crossover Evaluation of the Pharmacokinetics of Daptomycin and Aztreonam when Administered alone and when Administered in Combination in Normal Volunteers*"

09/05/01
IND 091

Addition of Investigators, Protocols DAP-00-05, VRE-00-07, DAP-CAP-00-08, DAP-HEP-00-09

	DAP-00-05	
	Hungary	
Dr. G. Nagy	Budapest, Hungary	DAP-00-05
	The Netherlands	
Dr. W.R. Pieters	Helmond, The Netherlands	DAP-00-05
	Russia	
Dr. M. V. Baluda	Moscow, Russia	DAP-00-05
Dr. P. G. Filippov	Moscow, Russia	DAP-00-05
Dr. N. P. Sanina	Moscow, Russia	DAP-00-05
Dr. L. B. Sokolova	Moscow, Russia	DAP-00-05
Dr. V. G. Novodzenov	Moscow, Russia	DAP-00-05
Dr. M. L. Zubkin	Moscow, Russia	DAP-00-05
	South Africa	
Dr. M. S. Abdool-Gaffar	Amanzimtoti, South Africa	DAP-00-05
Dr. I. A. Abdullah	Durban, South Africa	DAP-00-05
Dr. G. C. Ellis	Somerset West, South Africa	DAP-00-05
Dr. P. A. Hutton	Free State, South Africa	DAP-00-05
Dr. T. Smit	Wynberg, South Africa	DAP-00-05
Dr. F. Tun	Kimberley, South Africa	DAP-00-05
Dr. J.J. Viljoen	Free State, South Africa	DAP-00-05
Prof. P.A. Wilcox	Cape Town, South Africa	DAP-00-05
	Switzerland	
Dr. R. Grāni	Wolhusen, Switzerland	DAP-00-05
Dr. T. Kaeslin	Sarnen, Switzerland	DAP-00-05
	Spain	
Dr. J. M. Kindelán	Córdoba, Spain	DAP-00-05
	United States	
Dr. K. C. Wong	Glendale, CA	DAP-00-05
	DAP-VRE-00-07	
	United States	
Dr. W. Beliveau	Johnston, RI	DAP-VRE-00-07
Dr. J. Fraiz	Indianapolis, IN	DAP-VRE-00-07
Dr. Adrian James	New Orleans, LA	DAP-VRE-00-07
Dr. H. Kantor	Odessa, TX	DAP-VRE-00-07
Dr. C. Lynn V. Anderson	Bay Pines, FL	DAP-VRE-00-07
Dr. Donald H. Batts	Kalamazoo, MI	DAP-VRE-00-07
Dr. Bonnie V. Bock	Newport Beach, CA	DAP-VRE-00-07
Dr. Christopher F. Carpenter	Royal Oak, MI	DAP-VRE-00-07
Dr. Kerry O. Cleveland	Memphis, TN	DAP-VRE-00-07
Dr. Michael W. Climo	Richmond, VA	DAP-VRE-00-07
Dr. Brian W. Cooper	Hartford, CT	DAP-VRE-00-07
Dr. Lisa L. Dever	East Orange, NJ	DAP-VRE-00-07
Dr. Marcelo Gareca	Allentown, PA	DAP-VRE-00-07
Dr. Manjari Joshi	Baltimore, MD	DAP-VRE-00-07
Dr. Gary T. Kinasewitz	Oklahoma City, OK	DAP-VRE-00-07
Dr. Jay Ward Kislak	New York, NY	DAP-VRE-00-07
Dr. Mark H. Levin	Berwyn, IL	DAP-VRE-00-07
Dr. Peter K. Linden	Pittsburgh, PA	DAP-VRE-00-07
Dr. John Nowakowski	Valhalla, NY	DAP-VRE-00-07
Dr. Kenneth Rolston	Houston, TX	DAP-VRE-00-07
Dr. Robert G. Sawyer	Charlottesville, VA	DAP-VRE-00-07
Dr. Randi S. Silibovsky	Philadelphia, PA	DAP-VRE-00-07

		DAP-CAP-00-08 **Mexico**	
	Dr. José Ricardo Juárez Ocaña	Colonia Magdalena de las Salinas, México, D.F, México	DAP-CAP-00-08
		DAP-HEP-00-09 **United States**	
	Dr. Lawrence Galitz	Miami, Florida	DAP-HEP-00-09

10/09/01 **IND 092**	Pre-NDA Meeting Information Package for November 9th, 2001 Meeting with Cubist and the FDA
10/10/01 **IND 093**	Phase 1 Protocol DAP-MDRI-01-03 "*Evaluation of the Pharmacokinetic and Safety Profile of Multiple-Dose Daptomycin in Subjects with End-Stage Renal Disease on Hemodialysis*" and Pharmacokinetic Study Report for Phase 1 Study DAP-00-01
10/15/01 **IND 094**	Additional copies of Pre-NDA Meeting Information Package for November 9th, 2001
10/18/01 **IND 095**	Submission of Phase 1 Protocol DAP-MDRI-01-03 Amendment 1
10/19/01 **IND 096**	Submission of Protocol DAP-VRE-00-07, Amendment 2 and Minutes of the August 28, 2001 VRE Teleconference
10/31/01 **IND 097**	Phase 1 Protocol DAP-MDRI-01-09 "*Evaluation of the Pharmacokinetic and Safety Profile of Multiple-Dose Daptomycin in Subjects with Moderately Impaired Renal Function (CL_{cr} 30-50 mL/min)*" and Submission of Protocol DAP-MDRI-01-09 Amendment 1
10/31/01 **IND 098**	Phase 1 Protocol DAP-D1-01-01 "*A Double-Blind, Randomized, Three-Way, Crossover Evaluation of the Pharmacokinetics of Daptomycin and Aztreonam when Administered in Combination in Normal Volunteers*"
11/01/01 **IND 099**	Response to Agency's request for Daptomycin IND Safety Reports
11/01/01 **IND 100**	Submission of Protocol DAP-SST9901 Final Clinical Study Report
11/05/01 **IND 101**	Proposed Plan to Obtain Approved Labeling for Daptomycin in Patients with Severely Impaired Renal Function
11/09/01 **IND 102**	Submission of Protocol DAP-IE-01-02, "*A Phase 2/3, Multicenter, Randomized, Open-Label, Comparative Study to Assess the Safety and Efficacy of Daptomycin Compared to Conventional Therapy in the Treatment of Subjects with Complicated Bacteremia and Infective Endocarditis Due to* ***Staphylococcus aureus***" Request for Protocol Review
11/16/01 **FDA**	Fax from Agency with clarification of ISE and ISS positions from Pre-NDA meeting held November 9th, 2001
11/16/01 **FDA**	Fax from Agency with Statistical Comments for Protocol dated 11/17/00 Serial 062 (*"A Randomized, Double-Blind, Phase III, Comparative Study of Cidecin (Daptomycin) to Rocephin (Ceftriaxone) in the Treatment of Moderate to Severe Community-Acquired Acute Bacterial Pneumonia Due to S. Pneumonia")*
11/19/01 **FDA**	Fax from Agency with comments on latest CAP protocol (Serial 084)
11/26/01 **IND 103**	Addition of Investigators, Protocols DAP-SST9901, DAP-00-03, DAP-00-05, VRE-00-07, DAP-CAP-00-08 and MDRI-01-03

	DAP-SST9901	
	France	
Dr. Jamil Rahmani	Levallois-Perret, France	DAP-SST9901
	Germany	
Prof. Dr. med. Gerhard Fierlbeck	Tubingen, Germany	DAP-SST9901
	Russia	
Y. Belousov	Moscow, Russia	DAP-SST9901
E. Macheret	Moscow, Russia	DAP-SST9901
	DAP-00-03	
	Czech Republic	
Dr. Jareslav Hyncica[+]	Zlin, Czech Republic	DAP-00-03
Dr. Jiri Los[+]	Prerov, Czech Republic	DAP-00-03
Dr. Pavel Pauk[+]	Kladno, Czech Republic	DAP-00-03
	Greece	
Prof. John Kastriotis	Athens, Greece	DAP-00-03
	Hungary	
Gabor Bajor, M.D.	Budapest, Hungary	DAP-00-03
	DAP-00-05	
	Australia	
Dr. Marianne Chapman	Adelaide, Australia	DAP-00-05
Dr. David C. Sowden	Nambour, Australia	DAP-00-05
	Belgium	
Prof. Dr. De Backer, M.D.	Edegem, Belgium	DAP-00-05
	Canada	
Guy Tellier, M.D.	St. Jerome, Quebec	DAP-00-05
	France	
Dr. Eric Fournier	Henin-Beaumont, France	DAP-00-05
	Hungary	
Marta Bisits, M.D.	Tatabanya, Hungary	DAP-00-05
	Russia	
Prof. M.V. Baluda	Moscow, Russia	DAP-00-05
Prof. P.G. Filippov	Moscow, Russia	DAP-00-05
Prof. V.G. Novodzenov	Moscow, Russia	DAP-00-05
Dr. N.P. Sanina	Moscow, Russia	DAP-00-05
I.B. Sokolova, M.D.	Moscow, Russia	DAP-00-05
M.I. Zubkin, M.D.	Moscow, Russia	DAP-00-05
	South Africa	
Dr. J. Bouwer	Free State, S. Africa	DAP-00-05
Dr. M.J. Heystek	Mamelodi, S. Africa	DAP-00-05
Dr. S.A. Hitchcock	Atteridgeville, S. Africa	DAP-00-05
Dr. G. C. Ellis	Somerset West, S. Africa	DAP-00-05
Dr. G. C. Joynt	Witbank, S. Africa	DAP-00-05
Dr. J. Killian	Wilgers, S. Africa	DAP-00-05
Prof. U.G. Lalloo	Durban, S. Africa	DAP-00-05
Dr. F.W. Ogundare	Boksburg, S. Africa	DAP-00-05
Dr. T. Smit	Wynberg, S. Africa	DAP-00-05
Dr. L. van Zyl	Western Cape, S. Africa	DAP-00-05
	Sweden	
Dr. Jan Fohlman	Uppsala, Sweden	DAP-00-05
	Switzerland	
Prof. Dr. med Claude Regamey	Fribourg, Switzerland	DAP-00-05
	United States	
William Beliveau, M.D.	Johnston, RI	DAP-00-05
Dr. Joseph Fraiz	Indianapolis, IN	DAP-00-05
Adrian James, M.D.q	New Orleans, LA	DAP-00-05
Harvey Kantor, M.D.	Odessa, TX	DAP-00-05

	VRE-00-07	
	United States	
Ziad A. Akl, M.D.	Arlington, VA	VRE-00-07
David K. Bland, M.D	Loma Linda, CA	VRE-00-07
Christopher Carpenter, M.D.	Royal Oak, MI	VRE-00-07
Pranatharthi Chandrasekar, M.D.	Detroit, MI	VRE-00-07
Larry I. Emdur, D.O.	San Diego, CA	VRE-00-07
Vance Fowler, M.D.	Durham, N.C.	VRE-00-07
Shelley M. Gordon, M.D.	San Francisco, CA	VRE-00-07
Carol Kauffman, M.D.	Ann Arbor, MI	VRE-00-07
Mark H. Levin, M.D.	Berwyn, IL	VRE-00-07
Peter K. Linden, M.D.	Pittsburgh, PA	VRE-00-07
John F. Reinhardt, M.D.	Newark, DE	VRE-00-07
David R. Snydman, M.D.	Boston, MA	VRE-00-07
Byungse Suh, M.D.	Philadelphia, PA	VRE-00-07
Randall Walker, M.D.	Rochester, MN	VRE-00-07
	CAP-00-08	
	Chile	
Hernan Cabello, M.D.	Santiago, Chile	CAP-00-08
	Peru	
Pablo Ajejandro Grados Torres	Lima, Peru	CAP-00-08
	United States	
Dominick Soresso, M.D.	Hudson, FL	CAP-00-08
	MDRI-01-03	
	United States	
Dr. Lawrence Galitz	Miami, Florida	MDRI-01-03

11/26/01 IND 104	December 3, 2001 Meeting/Questions for Discussion Related to Protocol DAP-VRE-00-07
11/28/01 IND 105	Response to Statistical Comments on the Community Acquired Pneumonia (CAP) Studies with Daptomycin
11/29/01 IND 106	Submission of Phase 1 Protocol DAP-QTNC-01-06 "*A Randomized, Double-blind, Placebo-controlled Assessment of Peripheral Nerve Function and Cardiac Repolarization in Normal Volunteers Administered Daptomycin Intravenously Once Daily for 14 Days*" Form 1572 and CV for Dr. Galitz
11/29/01 IND 107	Submission of Phase 1 Protocol DAP-MDRI-01-09 "*Evaluation of the Pharmacokinetic and Safety Profile of Multiple-Dose Daptomycin in Subjects with Moderately Impaired Renal Function (CL_{cr} 30-50 mL/min)*" Amendment No. 2
11/30/01 Cubist	Email to Agency with Microsoft Word Document containing CMC questions for the December 3rd, 2001 meeting between the Agency and Cubist.
11/30/01 FDA	Fax from Agency with statistical questions/comments on VRE protocol (Serial Number 96)
11/30/01 IND 108	Submission of November 9th, 2001 Daptomycin Pre-NDA Meeting Minutes
12/07/01 Cubist	E-mail to agency informing them of Cubist decision to terminate the ongoing VRE trial and not pursue a VRE indication for daptomycin.
12/07/01 IND 109	Submission of Cubist's Minutes of December 3, 2001 Pre-NDA CMC Meeting
12/14/01 IND 110	Submission of Pharmacokinetic Report: DAP-00-01: "*Evaluation of the Elimination and Safety Profile of Daptomycin in Subjects with Graded Renal Insufficiency, End-stage Renal Disease and Healthy Volunteers.*"

12/14/01 IND 111	Submission of Clinical Study Report DAP-00-01: "*Evaluation of the Elimination and Safety Profile of Daptomycin in Subjects with Graded Renal Insufficiency, End-stage Renal Disease and Healthy Volunteers.*"
12/18/01 IND 112	Submission of Protocol DAP-VRE-00-07, December 3rd, 2001 Meeting Minutes
12/28/01 IND 113	Submission of Clinical Study Report DAP-00-02: "*A Randomized, Double-Blind, Multiple-Dose, Pharmacokinetic and Safety Study of Ascending Doses of Daptomycin in Healthy Volunteers.*"
01/03/02 IND 114	Submission of Protocols DAP-OBSE-01-07: *"A Single Dose Study to Evaluate the Pharmacokinetics and Safety of Cidecin® (daptomycin for injection) in obese subjects and non-obese matched subjects following a dose of 4mg/kg total body weight."*, DAP-STAT-01-10: *"A Randomized, double-Blind Study to Evaluate the Safety Profile of Multiple Dose Cidecin® (daptomycin for injection) in subjects on Zocor® (simvastatin)."* And DAP-GER-01-11: *"A Single Dose Study to evaluate the pharmacokinetics and safety of Cidecin® (daptomycin for injection) in healthy geriatric and younger healthy subjects following a dose of 4 mg/kg total body weight."*
01/15/02 IND 115	Submission of Protocol DAP-SST-9801-B "*An Open-Label, Non-Comparative Study to Evaluate the Pharmacokinetic, Safety and Efficacy of IV Daptomycin in Subjects with Complicated Skin and Soft Tissue Infections Due to Gram-Positive Bacteria.*"
01/16/02 IND 116	Submission of Protocol DAP-00-05 Study results.
02/07/02 IND 116*	Submission of Teleconference Minutes for Endocarditis DAP-IE-01-02 and VRE DAP-VRE-00-07 programs.
02/08/02 FDA	Letter from Agency informing Cubist to report IND submission 114, containing information about a new protocol, to the Clinical Trials Data Bank
02/14/02 IND 118	Submission of Request for Teleconference to Discuss NDA Filing Strategy for Daptomycin
02/22/02 IND 119	IND Initial Safety Report-Protocol DAP-QTNC-01-06
02/22/02 IND 120	Submission of DAP-IE-01-02, Amendment 1 / Request for Review
02/25/02 IND 121	Follow-up IND Initial Safety Report-Protocol DAP-QTNC-01-06
03/04/02 FDA	Fax from Agency with comments from a CDER internal meeting (February 25. 2002) on Cubist NDA filing
03/13/02 IND 122	Request for Additional Information Related to FDA Facsimile Dated March 4, 2002
03/19/02 IND 123	Submission of Phase 1 Protocol DAP-DIW-01-08: "Effects of Cidecin®(Daptomycin for Injection) on the Pharmacokinetics and Pharmacodynamics of Warfarin"
03/21/02 IND 124	Submission of Overheads from December 3, 2001, Pre-NDA CMC Meeting Minutes
03/21/02 IND 125	Submission of Teleconference Minutes/VRE (DAP-VRE-00-07) Program held December 20, 2001
03/25/02 IND 126	Submission of CD-ROMs for Protocol DAP-IE-01-02/Amendment 1

03/27/02 FDA	Email from Agency requesting Identification by number of CRF's that were a) endocarditis vs. bacteremia b) S. aureus, c) those which were labeled failures by Lilly (either dapto or comparator treated) on the AVAM CD-ROM
03/28/02 Cubist	Email to Agency with response to their request for information on the CRF's from Lilly's endocarditis Study B8B-MC-AVAM on March 27th, 2002
03/28/02 IND 127	Submission of DAP-HEP-00-09 "*A Comparison of the Pharmacokinetics of Cidecin (Daptomycin) in Subjects with Impaired Hepatic Function (Childs-Pugh B) and in Matched Healthy Volunteers*" Final Clinical Study report
03/28/02 IND 128	Submission of Cubist's third Annual Report
03/28/02 FDA	Email from Agency requesting patient classifications from Table 2-5 and Table 2-6, from Cubist submission 120, dated February 22, 2002
03/28/02 FDA	Email from Agency requesting a listing of the pk and tough levels for daptomycin based on the CRFs submitted, and copy of the original 1990 endocarditis study.
03/28/02 Cubist	Email to Agency with copy of Clinical Study Report B8B-MC-AVAM attached as a TIF file.
03/28/02 Cubist	Email to Agency with a tabulation of specific case numbers represented in Tables 2-5 and 2-6 of Protocol DAP-IE-01-02 and AVAM case numbers attached as a MS Word file.
04/08/02 IND 129	Submission of the FDA Response to IND Serial #122 (submission of safety data related to two CAP studies for complicated skin and skin structure infections)
04/12/02 FDA	Fax from Agency with comments from a CDER internal meeting (April 12, 2002) on Cubist Protocol DAP-IE-01-02
04/15/02 IND 130	Submission of DAP-VRE-00-07/Amendment No. 2
05/09/02 IND 131	Submission of Protocol DAP-IE-01-02, Amendment 2
05/10/02 IND 132	Addition of Investigators, Protocols DAP-CAP-00-08

		CAP-00-08
	Argentina	
Javier Altclas, M.D.	Buenos Aires, Argentina	CAP-00-08
Guillermo Benchetrit, M.D.	Buenos Aires, Argentina	CAP-00-08
Cristina De Salvo, M.D.	Buenos Aires, Argentina	CAP-00-08
Alberto Dolmann, M.D.	Buenos Aires, Argentina	CAP-00-08
Jorge Gentile, M.D.	Tandil, Argentina	CAP-00-08
Lucia Marzoratti, M.D.	Tucuman, Argentina	CAP-00-08
Susana Nahabedian	Buenos Aires, Argentina	CAP-00-08
Guillermo Recupero, M.D.	Tucuman, Argentina	CAP-00-08
Cesar Benito Saenz, M.D.	Buenos Aires, Argentina	CAP-00-08
Luis Fernando Vega, M.D.	Posadas Misiones, Argentina	CAP-00-08
	Brazil	
Luis Eduardo Mendes Campos, M.D.	Belo Horizonte, MG, Brazil	CAP-00-08
Joao Carlos Correa, M.D.	Rio de Janeiro, RJ, Brazil	CAP-00-08
Alvaro A. Cruz, M.D.	Salvador, Bahia, Brazil	CAP-00-08
Dagoberto Vanoni de Godoy, M.D.	Caxius do Sul, RS, Brazil	CAP-00-08
Waldo Luis Leite Dias de Mattos, M.D	Porto Allegre, RS, Brazil	CAP-00-08

Jose Wellington Alves dos Santos, M.D.	Santa Maria, RS, Brazil	CAP-00-08
Fernando Lundgren, M.D.	Recife, PE, Brazil	CAP-00-08
Maria Auxiliadora Carmo Moreira, M.D.	Goiânia, Góiás, Brazil	CAP-00-08
Roberto Stibulov, M.D.	São Paulo, SP, Brazil	CAP-00-08
Paulo Zimermann Teixeira, M.D.	Porto Alegre, RS, Brazil	CAP-00-08
	Bulgaria	
Dimitar Dimitrov, M.D.	Sofia, Bulgaria	CAP-00-08
Ognyun Georgiev, M.D.	Sofia, Bulgaria	CAP-00-08
Rosen Georgiev, M.D.	Sofia, Bulgaria	CAP-00-08
Hristo Metev, M.D.	Russe, Bulgaria	CAP-00-08
Dimitar Popov, M.D.	Sofia, Bulgaria	CAP-00-08
	Chile	
Maria Isabel Campos Barker	Santiago, Chile	CAP-00-08
Rebeca Northland, M.D	Santiago, Chile	CAP-00-08
Fernando Saldías, M.D.	Santiago, Chile	CAP-00-08
	Mexico	
Germán Vargas Ayala, M.D.	Mexico, DF, Mexico	CAP-00-08
Simón Hernández Campos, M.D.	Durango, Mexico	CAP-00-08
Jesús Ernesto Casillas Cancino, M.D.	Mexico, DF, Mexico	CAP-00-08
Martin Alberto Herrera Cornejo, M.D.	Mexico, DF, Mexico	CAP-00-08
Mauricio Ibañez del Campo, M.D.	Mexico, DF, Mexico	CAP-00-08

05/22/02 FDA	Fax from Agency with the Pre-NDA Meeting minutes, held November 9, 2001
05/30/02 FDA	Fax from Agency with comments from the Division's internal daptomycin meeting held on May 29, 2002 with issues regarding the VRE/endocarditis issues.
05/31/02 Cubist	Submission of Protocol DAP-IE-01-02, Amendment 1/Meeting Minutes via email
05/31/02 IND 133	Submission of Protocol DAP-IE-01-02, Amendment 1/Meeting Minutes including slides
06/06/02 Cubist	Submission of IND Initial Safety Report- Protocol DAP-CAP-00-08 via email
06/06/02 IND 134	Submission of IND Initial Safety Report- Protocol DAP-CAP-00-08
06/14/02 IND 135	Submission of Cubist's response to Daptomycin Pre-NDA Meeting Request, including an electronic list of patient identification numbers for Phase 3 Daptomycin clinical trials.
06/14/02 IND 136	Submission of Cubist's response to Agency request for Clarification for Protocol DAP-QTNC-01-06
07/02/02 Cubist	Memo of Teleconference with Dr. Sue Chih Lee (FDA Clinical Pharmacologist) on DAP-DIW-01-08 "Precaution Section"
07/05/02 IND 137	Submission of Endocarditis and VRE teleconference held on May 31, 2002
07/10/02 IND 138	Submission of minutes of FDA Teleconference / VRE (DAP-VRE-00-07, Amendment 2) Program

07/25/02 FDA	E-mail from Agency with request to resubmit Submission number 135 as Electronic submission.
07/29/02 IND 139	Response to Daptomycin Pre-NDA Meeting Request/SAS Xport Transport files. Sent as electronic submission.
08/06/02 FDA	Fax from Agency with meeting minutes for End of Phase 2 Meeting CMC held May 12, 2000, meeting on CMC Technical Data Section held December 3, 2001, meeting on VRE program held December 20, 2001, and endocarditis clinical trial and VRE program held January 16, 2002.
8/22/02 FDA	Internal e-mail from Agency with request for instructions on opening .xpt files sent as Submission 139
08/23/02 IND 140	Addition of Investigators, Protocols DAP-IE-01-02 and DAP-VRE-00-07

	DAP-IE-01-02	
Gio Baracco, M.D.+	Miami, FL	DAP-IE-01-02
Jack M. Bernstein, M.D.+	Dayton, OH	DAP-IE-01-02
Suzanne F. Bradley, M.D.	Ann Arbor, MI	DAP-IE-01-02
Paul P. Cook, M.D.	Greenville, NC	DAP-IE-01-02
Marcelo Gareca, M.D.+	Allentown, PA	DAP-IE-01-02
Daniel M. Goodenberger, M.D.+	St. Louis, MO	DAP-IE-01-02
Kevin High, M.D.+	Winston-Salem, NC	DAP-IE-01-02
Donald P. Levine, M.D.+	Detroit, MI	DAP-IE-01-02
Frank Lowy, M.D.+	New York, NY	DAP-IE-01-02
Mark E. Rupp, M.D.+	Omaha, NE	DAP-IE-01-02
Jane R Schwebke, M.D.+	Birmingham, AL	DAP-IE-01-02
Louis Sloan, M.D.+	Dallas, TX	DAP-IE-01-02
James S. Tan, M.D.+	Akron, OH	DAP-IE-01-02
Alan Tice, M.D.+	Honolulu, HI	DAP-IE-01-02
	DAP-VRE-00-07	
Michael Aronoff, M.D.+	Boston, MA	DAP-VRE-00-07
Gregory J. Beilman, M.D.	Minneapolis, MN	DAP-VRE-00-07
David S. McKinsey, M.D.	Kansas City, MO	DAP-VRE-00-07
Annette Reboli, M.D.	Camden, NJ	DAP-VRE-00-07

8/26/02 Cubist	E-mail to Agency with request for clarification as to specific daptomycin clinical trials the division would like to random sample from and response to Agency problems with SAS transport files.
09/04/02 Cubist	E-mail to Agency regarding amendments to Clinical Study Reports. (micro listings and histograms in the appendices to Clinical Study Report DAP-SST-9901.)
09/05/02 FDA	E-mail from Agency with answer to Cubist E-mail sent to the agency on September 4, 2002 regarding Clinical Study Report DAP-SST-9901
09/13/02 IND 141	Submission of Daptomycin Target Package Insert
09/23/02 IND 142	Submission of Protocol DAP-EAP-02-01 *"A Treatment Protocol for Intravenous Daptomycin, for the Treatment of Infections due to Gram-Positive Bacteria that cannot be adequately Treated with Currently Available Therapy"*
09/23/02 IND 143	Submission of Revised SAS Transport Files
09/24/02 IND 144	Submission of Modified Informed Consent Form template for the endocarditis clinical study, Protocol No. DAP-IE-01-02
09/25/02 IND 145	Submission of Protocol DAP-VRE-00-07/Amendment No. 3

09/26/02 IND 146	Addition of Investigators, Protocols DAP-BAC-9803, DAP-RRC-9804, DAP-IE-01-02 and DAP-VRE-00-07		
		DAP-BAC-9803	
	Gary R. Decker, M.D.+	Wilkes-Barre, PA	DAP-BAC-9803
		DAP-RRC-9804	
	Ian M. Baird, M.D., FACP+	Columbus, OH	DAP-RRC-9804
		DAP-VRE-00-07	
	John Baddley, M.D.	Birmingham, AL	DAP-VRE-00-07
	Jerome Levine, M.D.	Hackensack, NJ	DAP-VRE-00-07
	John C. Schaefer, M.D.	Norfolk, VA	DAP-VRE-00-07
	John Segreti, M.D.	Chicago, IL	DAP-VRE-00-07
	Gary Leonard Simon, M.D., PhD	Washington, D.C.	DAP-VRE-00-07
		DAP-IE-01-02	
	Helmut Albrecht, M.D.	Atlanta, GA	DAP-IE-01-02
	Robert Betts, M.D.	Rochester, NY	DAP-IE-01-02
	Thomas Claffey, M.D.	S. Portland, ME	DAP-IE-01-02
	Ellie Hershberger, PharmD	Royal Oak, MI	DAP-IE-01-02
	Marcus J. Zervos, M.D.	Royal Oak, MI	DAP-IE-01-02
09/27/02 Cubist	Submission of Pediatric Waiver via Facsimile to John Alexander at the Agency		
09/27/02 IND 147	Submission of Pediatric Waiver		
10/01/02 IND 148	Submission of revised request for Pediatric Waiver		
10/03/02 FDA	E-mail from Agency stating that Cubist formally request a meeting to discuss questions including Daptomycin Target Package Insert		
10/04/02 IND 149	Submission of Request for Meeting/Teleconference to Discuss the Target Package Insert for Daptomycin.		
10/09/02 IND 150	Submission of Request for Clarification to questions on the Target Package Insert, Daptomycin NDA and Emergency Use Program.		
10/10/02 IND 151	Submission of September 12, 2002 CMC Teleconference Minutes		
10/10/02 IND 152	Submission of General Correspondence - Waiver Request for Population PK NDA section		
10/21/02 FDA	Fax from Agency with the 10% random sample of SST9801		
10/31/02 IND 153	Addition of Investigators, Protocols DAP-IE-01-02, and DAP-VRE-00-07		
		DAP-IE-01-02	
	Henry Chambers, M.D.	San Francisco, CA	DAP-IE-01-02
	Kerry Cleveland, M.D.	Memphis, TN	DAP-IE-01-02
	Graeme Forrest, MBBS	Baltimore, MD	DAP-IE-01-02
	Dennis Maki, M.D.	Madison, WI	DAP-IE-01-02
		DAP-VRE-00-07	
	Robert Betts, M.D.	Rochester, NY	DAP-VRE-00-07
	Ali El-Solh, M.D.	Buffalo, NY	DAP-VRE-00-07
	Daniel Hinthorn, M.D.	Kansas City, KS	DAP-VRE-00-07
	Mir Hasain, M.D.	Peoria, IL	DAP-VRE-00-07
	Julio Ramirez, M.D.	Louisville, KY	DAP-VRE-00-07
10/21/02 IND 154	Submission of Emergency Use Request Teleconference Minutes		

12/03/02 FDA	Fax from Agency with outstanding issues related to VRE, endocarditis trials, Package Insert, Emergency Use and Population PK waiver request.
12/09/02 IND 155	Submission of Information Update designating David Schubert as Vice President, Regulatory Affairs and Quality, Cubist Pharmaceuticals, Inc.
12/09/02 IND 156	Addition of Investigators, Protocols DAP-IE-01-02, and DAP-VRE-00-07

	DAP-IE-01-02	
Keith Barclay Armitage, M.D.	Cleveland	DAP-IE-01-02
John Baddley, M.D.	Birmingham, AL	DAP-IE-01-02
Scott Filler, M.D.	Torrance, CA	DAP-IE-01-02
Peter Krumpe, M.D.	Reno, NV	DAP-IE-01-02
Christian Shrock, M.D.	Minneapolis, MN	DAP-IE-01-02
John Segreti, M.D.	Chicago, IL	DAP-IE-01-02
R. Scott Stienecker M.D.	Lima, OH	DAP-IE-01-02
	DAP-VRE-00-07	
John Daller, M.D.	Galveston, TX	DAP-VRE-00-07
Jennifer Janelle, M.D.	Gainesville, FL	DAP-VRE-00-07
Anne Mosenthal, M.D., FACS	Newark, NJ	DAP-VRE-00-07
Richard Prokesch	Riverdale, GA	DAP-VRE-00-07

12/18/02 IND 157	Submission of Updated Investigator's Brochure (IB) Version 4. Dated December 2002.
01/17/03 IND 158	Submission of Cubist Community-Acquired Pneumonia (CAP) Amendment
01/24/03 IND 159	Submission of Protocol DAP-EAP-02-01/Amendment No 1
01/31/03 IND 160	Addition of Investigators, Protocols DAP-IE-01-02, and DAP-VRE-00-07

	DAP-IE-01-02	
Mujahed Abbas, M.D.	Detriot, MI	DAP-IE-01-02
Kerry Cleveland, M.D.	Memphis, TN	DAP-IE-01-02
E. Dale Everett, M.D.	Columbia, MO	DAP-IE-01-02
Donald Graham, M.D.	Springfield, IL	DAP-IE-01-02
Bruce Hirsch, M.D.	Manhasset, NY	DAP-IE-01-02
Matthew Levison, M.D.	Philadelphia, PA	DAP-IE-01-02
Jeffrey Parsonnet, M.D.	Lebanon, NH	DAP-IE-01-02
Glenn Turett, M.D.	New York, NY	DAP-IE-01-02
	DAP-VRE-00-07	
Mir Husain, M.D.	Peoria, IL	DAP-VRE-00-07
Gary Kinasewitz, M.D.	Oklahoma City, OK	DAP-VRE-00-07
Kenneth Rolston, M.D.	Houston, TX	DAP-VRE-00-07

02/05/03 IND 161	Submission of Emergency Use Memo dated February 3, 2003
02/12/03 IND 162	Submission of Investigator's Brochure Version 4.1 dated February 11, 2003
02/21/03 FDA	Fax from Agency with Statistical Comments for DAP-EAP-02-01 (Serial #159) dated January 27, 2003.
02/21/03 Cubist	FDA Call Report regarding Treatment Use Protocol
02/26/03 Cubist	FDA Call Report regarding clarification of February 21, 2003 fax from Agency with Statistical Comments for DAP-EAP-02-01

03/06/03 IND 163	General Correspondence to the Agency with notice that the 120-day safety update and the Annual Report will be submitted simultaneously on April 18, 2003.
03/10/03 IND 164	Submission of Protocol DAP-REN-02-03.
03/13/03 IND 165	Submission of Protocol DAP-EAP-01-02/Amendment 2 (Compassionate Use) along with notification of DAP-VRE-007 closing
03/21/03 IND 166	Submission of internal memo regarding IRB notification by physicians who treated patients on an emergency use basis.
03/24/03 IND 167	Submission of Protocol DAP-MDRI-01-03/Clinical Study Report
04/02/03 IND 168	Submission of Protocol DAP-REN-02-03/Amendment No. 1
04/02/03 IND 169	Submission of Protocol DAP-IE-01-02/Amendment No. 3
04/03/03 IND 170	Submission of Protocol DAP-00-04 CSR
04/04/03 IND 171	Change in Manufacturing Site for Daptomycin Drug Substance
04/04/03 IND 172	Submission of Protocol DAP-GER-01-11 CSR
04/14/03 IND 173	Submission of Protocol DAP-BAC-98-03 CSR
04/14/03 IND 174	Submission of Protocol DAP-MDRI-01-09 CSR
04/29/03 IND 175	Submission of Cubist's 4th Annual Report
04/29/03 IND 176	Investigator Update. Protocols DAP-SST-9801-B and DAP-VRE-007

	DAP-VRE-00-07	
Prof. J.E.J. Krige	Cape Town, South Africa	DAP-SST-9801-B
	DAP-VRE-00-07	
John Baddley, MD*	Birmingham,AL	DAP-VRE-00-07
Mark Levin, MD*	Berwyn, IL	DAP-VRE-00-07
Annette Reboli, MD*	Camden, NJ	DAP-VRE-00-07
John Schaefer, MD*	Norfolk, VA	DAP-VRE-00-07
Harold Standiford, MD	Baltimore, MD	DAP-VRE-00-07
Byungse Suh, MD, PhD*	Philadelphia, PA	DAP-VRE-00-07

05/07/03 IND 177	Response to FDA Request for Information (DAP-REN-02-03)
05/07/03 IND 178	15-day IND Safety Report – Initial (Protocol DAP-REN-02-03)
05/12/03 IND 179	Submission of Protocol DAP-IE-01-02/Amendment 3A
05/13/03 Cubist	Email to the Agency from D. Schubert with attached list of Cubists Amendment Numbering.

05/13/03 FDA	Acknowledgement Email from Raquel Peat regarding attached list of Cubists Amendment Numbering.
05/13/03 Cubist	Acknowledgement Email from D. Schubert regarding attached list of Cubists Amendment Numbering.
05/13/03 Cubist	Additional Email to the Agency from D. Schubert with attached list of Cubists Amendment Numbering.
--/--/-- IND 180*	*** This IND # was skipped per the FDA**
05/28/03 IND 181	15-day Follow-up Safety Report-Protocol DAP-REN-02-03
06/23/03 IND 182	General Correspondence/Transfer of Responsibilities (Meri Bloom)
08/01/03 IND 183	Investigator Update (DAP-IE-01-02 and DAP-REN-020-03

DAP-IE-01-02

Julio Figeuroa II, M.D.	New Orleans, LA	DAP-IE-01-02
Andrea Gabrielli, M.D.	Gainesville, FL	DAP-IE-01-02
Stephen Greenberg, M.D.	Houston, TX	DAP-IE-01-02
Daniel Hinthorn, M.D.	Kansas City, KS	DAP-IE-01-02
Mark Holodiny, M.D., FACP, CIC	Palo Alto, CA	DAP-IE-01-02
Harry Lampris, M.D.	San Francisco, CA	DAP-IE-01-02
Susan Rehm, M.D., FACP, FIDSA	Cleveland, OH	DAP-IE-01-02
W. Michael Scheld, M.D.	Charlottesville, VA	DAP-IE-01-02
David Snydman, M.D.	Boston, MA	DAP-IE-01-02

DAP-REN-02-03

Suzanne Swan, M.D.	Minneapolis, MN	DAP-REN-02-03

08/08/03 IND 184	Submission of clinical study DAP-DIW-01-08 *"Effects of Cidecin® Daptomycin for Injection) on the Pharmacokinetics and Pharmacodynamics of Warfarin"*
08/08/03 IND 185	Submission of clinical study DAP-DI-01-01 *"A Double-Blind, Randomized, Three-Way Crossover Evaluation of the Pharmacokinetics of Daptomycin and Aztreonam When Administered Alone and When Administered in Combination in Normal Volunteers"*
08/12/03 IND 186	Submission of clinical study DAP-SST-9801: *"A Multicenter, Investigator-Blinded, Randomized Study to Compare the Safety and Efficacy of IV Daptomycin With That of Vancomycin or a Semi-synthetic Penicillin in the Treatment of Complicated Bacterial Skin and Soft Tissue Infections due to Gram-Positive Bacteria"*
08/12/03 IND 187	Submission of clinical study DAP-00-02: *"A Randomized, Double-blind, Multiple Dose, Pharmacokinetic and Safety Study of Ascending Doses of Daptomycin in Healthy Volunteers".*
08/19/03 IND 188	Initial Safety Report- Protocol DAP-REN-02-03

08/26/03 IND 189	Protocol DAP-STAT-01-10/Clinical Study Report
08/26/03 IND 190	Protocol DAP-QTNC-01-06/Clinical Study Report
10/21/03 IND 191	Protocol DAP-SST-99-01/Clinical Study Report
10/21/03 IND 192	Protocol DAP-RRC-98-04/Clinical Study Report

EXHIBIT F

Power of Attorney

EXHIBIT F
Attorney Docket No.: IP085

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.:	4,885,243
Issued Date:	December 5, 1989
Applicants:	Floyd M. Huber et al.
Application No.:	773,762
Filed:	September 9, 1985
For:	PROCESS FOR PRODUCING A-21978C DERIVATIVES

POWER OF ATTORNEY

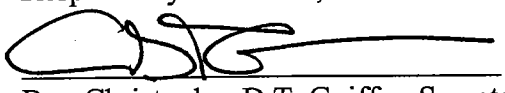
Commissioner for Patents
Alexandria, VA 22313-1450

Sir:

In connection with the above-identified application the undersigned Applicant hereby appoints Timothy J. Douros Registration No. 41,716 c/o CUBIST PHARMACEUTICALS, INC., 65 Hayden Avenue, Lexington, Massachusetts 02421, an attorney and/or agent, to prosecute this application, to make alterations and amendments therein, to receive the patent and to transact all business in the Patent and Trademark Office connected therewith.

All communications in connection with the prosecution of the above-identified application should be sent to Timothy J. Douros, Esq. c/o Cubist Pharmaceuticals, Inc., 65 Hayden Avenue, Lexington, Massachusetts 02421.

Respectfully submitted,



By: Christopher D.T. Guiffre, Secretary
For: Cubist Pharmaceuticals, Inc.
(781) 860-8660
Dated: November 10, 2003

PTO/SB/17 (10-03)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☑ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 1,120

Complete if Known	
Patent Number	US Patent 4,885,243
Issue Date	December 5, 1989
First Named Inventor	Floyd M. Huber et al.
Examiner Name	
Art Unit	
Attorney Docket No.	IP085

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☑ Deposit Account:

Deposit Account Number: 50-1986

Deposit Account Name: Cubist Pharmaceuticals

The Director is authorized to: *(check all that apply)*

☑ Charge fee(s) indicated below ☑ Credit any overpayments

☑ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below	Fee Paid
Total Claims	-20** =	X		=
Independent Claims	- 3** =	X		=
Multiple Dependent				=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	
Other fee (specify) Extension of Term of Patent					1,120

*Reduced by Basic Filing Fee Paid **SUBTOTAL (3)** ($) 1,120

SUBMITTED BY				(Complete *(if applicable)*)	
Name (Print/Type)	Timothy J. Douros	*Registration No. (Attorney/Agent)*	41,716	*Telephone*	781-860-8476
Signature	Timothy J. Douros			*Date*	November 10, 2003

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

This collection of information is required by 37 CFR 1.17 and 1.27. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/17 (10-03)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☑ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 1,120

Complete if Known	
Patent Number	US Patent 4,885,243
Issue Date	December 5, 1989
First Named Inventor	Floyd M. Huber et al.
Examiner Name	
Art Unit	
Attorney Docket No.	IP085

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☑ Deposit Account:

Deposit Account Number: 50-1986

Deposit Account Name: Cubist Pharmaceuticals

The Director is authorized to: *(check all that apply)*

☑ Charge fee(s) indicated below ☑ Credit any overpayments

☑ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below		Fee Paid
Total Claims		-20** =		X	=
Independent Claims		- 3** =		X	=
Multiple Dependent					=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) Extension of Term of Patent 1,120

*Reduced by Basic Filing Fee Paid **SUBTOTAL (3)** ($) 1,120

SUBMITTED BY				(Complete *(if applicable)*)	
Name (Print/Type)	Timothy J. Douros	*Registration No. (Attorney/Agent)*	41,716	*Telephone*	781-860-8476
Signature	Timothy J. Douros			*Date*	November 10, 2003

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PTO/SB/17 (10-03)
Approved for use through 07/31/2006. OMB 0651-0032
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FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☑ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 1,120

Complete if Known	
Patent Number	US Patent 4,885,243
Issue Date	December 5, 1989
First Named Inventor	Floyd M. Huber et al.
Examiner Name	
Art Unit	
Attorney Docket No.	IP085

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☑ Deposit Account:

Deposit Account Number: 50-1986

Deposit Account Name: Cubist Pharmaceuticals

The Director is authorized to: *(check all that apply)*

☑ Charge fee(s) indicated below ☑ Credit any overpayments

☑ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below	Fee Paid
Total Claims		-20** =		X =
Independent Claims		- 3** =		X =
Multiple Dependent				=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
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Other fee (specify) Extension of Term of Patent 1,120

*Reduced by Basic Filing Fee Paid **SUBTOTAL (3)** ($) 1,120

SUBMITTED BY				(Complete *(if applicable)*)	
Name (Print/Type)	Timothy J. Douros	*Registration No. (Attorney/Agent)*	41,716	*Telephone*	781-860-8476
Signature	Timothy J. Douros			*Date*	November 10, 2003

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This collection of information is required by 37 CFR 1.17 and 1.27. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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