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(42) *Tobramycin*. A specific one of the antibiotic substances produced by the growth of *Streptomyces tenebrarius*, and the same substance produced by any other means, is tobramycin.

(43) *Amikacin*. Each of the antibiotic substances produced by the acylation of the 1-amino group of the anhydro-streptamine moiety of kanamycin A with L-(+)- γ -amino- α -hydroxybutyric acid, and each of the same substances produced by any other means, is a kind of amikacin.

(44) *Vidarrabine*. Vidarrabine is a purine glycoside antibiotic substance produced by the growth of *Streptomyces antibioticus*, and each of the same substances produced by any other means is a kind of vidarrabine.

(45) *Nalamyacin*. Each of the antibiotic substances produced by the growth of *Streptomyces natalensis*, and each of the same substances produced by any other means, is a kind of nalamyacin.

(46) *Daurorubicin*. Each of the antibiotic substances produced by the growth of *Streptomyces coelicolor* var. *auricularis*, and each of the same substances produced by any other means, is a kind of daurorubicin.

(47) *Sisomicin*. A specific one of the antibiotic substances produced by the growth of *Micromonospora inyoensis*, and the same substance produced by any other means, is a kind of sisomicin.

(48) *Moxalactam*. 5-oxa-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, and each of the same substances produced by any other means, is a kind of moxalactam.

(49) *Cefoperazone*. Cefoperazone is a semi-synthetic antibiotic substance produced by the acylation of the amino group at the 7 position of 7-aminocephalosporanic acid with α -(4-hydroxyphenyl)acetyl-L-lysine.

(50) *Netilmicin*. Netilmicin is a semi-synthetic antibiotic of the aminoglycoside group derived from sisomicin, and each of the same substances produced by any other means is a kind of netilmicin. It is D-Streptamine, 4-O-13-

(51) *Cyclosporine*. Cyclosporine is a specific cyclic polypeptide consisting of 11 amino acids produced by the growth of *Cyathrocarpus lucidum* Booth or *Toypocladium infatum* Gams.

(52) *Cefonicid*. 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, and each of the same substances produced by any other means, is a kind of cefonicid.

(53) *Clavulanic acid*. Clavulanic acid is an antibiotic substance produced by the growth of *Streptomyces clavulifer* genus having the structure described as follows: 2-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[4.2.0]heptane-2-carboxylic acid, and each of the same substances produced by any other means, is a kind of clavulanic acid.

(54) *Ceftriaxone*. Ceftriaxone is a semi-synthetic antibiotic substance produced by the addition of S-2-benzothiazoyl-2-(2-aminothiazol-4-yl)-2-methoxyiminodiacetate to the 7-amino group of 7-amino-3-(2,5-dihydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl)-thiomethyl-3-cephem-4-carboxylic acid.

(55) *Netilmicin*. Each of the antibiotic substances produced by the growth of *Streptomyces lincolnensis* var. *lincolnensis*, and each of the same substances produced by any other means, is a kind of netilmicin. Each of the antibiotic substances produced by the growth of *Streptomyces verticillius* and each of the same substances produced by any other means is a kind of bleomycin.

standard of comparison in determining the potency of the streptomycin working standard.

(3) *Dihydrostreptomycin*. The term "dihydrostreptomycin master standard" means a specific lot of crystalline dihydrostreptomycin that is designated by the Commissioner as the standard of comparison in determining the potency of the dihydrostreptomycin working standard.

(4) *Chlortetracycline*. The term "chlortetracycline master standard" means a specific lot of crystalline chlortetracycline hydrochloride that is designated by the Commissioner as the standard of comparison in determining the potency of the chlortetracycline working standard.

(5) *Demeclocycline*. The term "demeclocycline master standard" means a specific lot of crystalline demeclocycline hydrochloride that is designated by the Commissioner as the standard of comparison in determining the potency of the demeclocycline working standard.

(6) *Tetracycline*. The term "tetracycline master standard" means a specific lot of crystalline tetracycline hydrochloride that is designated by the Commissioner as the standard of comparison in determining the potency of the tetracycline working standard.

(7) *Rolitetracycline*. The term "rolitetracycline master standard" means a specific lot of crystalline rolitetracycline that is designated by the Commissioner as the standard of comparison in determining the potency of the rolitetracycline working standard.

(8) *Chloramphenicol*. The term "chloramphenicol master standard" means a specific lot of crystalline chloramphenicol that is designated by the Commissioner as the standard of comparison in determining the potency of the chloramphenicol working standard.

(9) *Bacitracin*. The term "bacitracin master standard" means a specific lot of bacitracin that is designated by the Commissioner as the standard of comparison in determining the potency of the bacitracin working standard.

(10) *Amphoterycin*. The term "amphoterycin master standard" means a specific lot of amphoterycin designated by the Commissioner as the standard

of comparison in determining the potency of the amphoterycin working standard.

(11) *Amphotericin*. The term "amphotericin A master standard" means a specific lot of amphotericin A designated by the Commissioner as the standard of comparison in determining the potency of the amphotericin A working standard. The term "amphotericin B master standard" means a specific lot of amphotericin B designated by the Commissioner as the standard of comparison in determining the potency of the amphotericin B working standard.

(12) *Colistin*. The term "colistin master standard" means a specific lot of colistin designated by the Commissioner as the standard of comparison in determining the potency of the colistin working standard.

(13) *Colistimethate*. The term "colistimethate master standard" means a specific lot of colistimethate designated by the Commissioner as the standard of comparison in determining the potency of the colistimethate working standard.

(14) *Cycloserine*. The term "cycloserine master standard" means a specific lot of cycloserine designated by the Commissioner as the standard of comparison in determining the potency of the cycloserine working standard.

(15) *Erythromycin*. The term "erythromycin master standard" means a specific lot of erythromycin designated by the Commissioner as the standard of comparison in determining the potency of the erythromycin working standard.

(16) *Gramicidin*. The term "gramicidin master standard" means a specific lot of gramicidin designated by the Commissioner as the standard of comparison in determining the potency of the gramicidin working standard.

(17) *Grisofulvin*. The term "grisofulvin master standard" means a specific lot of grisofulvin designated by the Commissioner as the standard of comparison in determining the potency of the grisofulvin working standard.

(18) *Kanamycin*. The term "kanamycin master standard" means a specific lot of kanamycin designated by the Commissioner as the standard of

comparison in determining the potency of the kanamycin working standard.

(19) *Neomycin*. The term "neomycin master standard" means a specific lot of neomycin designated by the Commissioner as the standard of comparison in determining the potency of the neomycin working standard.

(20) *Novobiocin*. The term "novobiocin master standard" means a specific lot of novobiocin designated by the Commissioner as the standard of comparison in determining the potency of the novobiocin working standard.

(21) *Nystatin*. The term "nystatin master standard" means a specific lot of nystatin designated by the Commissioner as the standard of comparison in determining the potency of the nystatin working standard.

(22) *Oleandomycin*. The term "oleandomycin master standard" means a specific lot of oleandomycin designated by the Commissioner as the standard of comparison in determining the potency of the oleandomycin working standard.

(23) *Oxytetracycline*. The term "oxytetracycline master standard" means a specific lot of oxytetracycline designated by the Commissioner as the standard of comparison in determining the potency of the oxytetracycline working standard.

(24) *Paromomycin*. The term "paromomycin master standard" means a specific lot of paromomycin designated by the Commissioner as the standard of comparison in determining the potency of the paromomycin working standard.

(25) *Polymyxin B*. The term "polymyxin B master standard" means a specific lot of polymyxin B designated by the Commissioner as the standard of comparison in determining the potency of the polymyxin B working standard.

(26) [Reserved]

(27) *Vancomycin*. The term "vancomycin master standard" means a specific lot of vancomycin designated by the Commissioner as the standard of comparison in determining the potency of the vancomycin working standard.

(28) [Reserved]

(29) *Troleandomycin*. The term "troleandomycin master standard" means a specific lot of troleandomycin designated by the Commissioner as the standard of comparison in determining the potency of the troleandomycin working standard.

(30) *Gentamicin*. The term "gentamicin master standard" means a specific lot of gentamicin designated by the Commissioner as the standard of comparison in determining the potency of the gentamicin working standard.

(31) *Dactinomycin*. The term "dactinomycin master standard" means a specific lot of dactinomycin designated by the Commissioner as the standard of comparison in determining the potency of the dactinomycin working standard.

(32) *Candididin*. The term "candididin master standard" means a specific lot of candididin that is designated by the Commissioner as the standard of comparison in determining the potency of the candididin working standard.

(33) *Cephalothin*. The term "cephalothin master standard" means a specific lot of cephalothin designated by the Commissioner as the standard of comparison in determining the potency of the cephalothin working standard.

(34) *Lincomycin*. The term "lincomycin master standard" means a specific lot of lincomycin designated by the Commissioner as the standard of comparison in determining the potency of the lincomycin working standard.

(35) *Methacycline*. The term "methacycline master standard" means a specific lot of methacycline designated by the Commissioner as the standard of comparison in determining the potency of the methacycline working standard.

(36) *Doxycycline*. The term "doxycycline master standard" means a specific lot of 6-deoxyoxytetracycline designated by the Commissioner as the standard of comparison in determining the potency of the doxycycline working standard.

(37) *Cephaloridine*. The term "cephaloridine master standard" means a specific lot of cephaloridine that is designated by the Commissioner as

the standard of comparison in determining the potency of the cephaloridine working standard.

(38) *Plicamycin*. The term "plicamycin master standard" means a specific lot of plicamycin designated by the Commissioner as the standard of comparison in determining the potency of the plicamycin working standard.

(39) *Citrandamycin*. The term "clindamycin master standard" means a specific lot of clindamycin designated by the Commissioner as the standard of comparison in determining the potency of the clindamycin working standard.

(40) *Cephaloglycin*. The term "cephaloglycin master standard" means a specific lot of cephaloglycin designated by the Commissioner as the standard of comparison in determining the potency of the cephaloglycin working standard.

(41) *Carbenticillin*. The term "carbenticillin master standard" means a specific lot of carbenticillin designated by the Commissioner as the standard of comparison in determining the potency of the carbenticillin working standard.

(42) *Cephalexin*. The term "cephalexin master standard" means a specific lot of cephalexin that is designated by the Commissioner as the standard of comparison in determining the potency of the cephalexin working standard.

(43) [Reserved]

(44) *Capreomycin*. The term "capreomycin master standard" means a specific lot of capreomycin designated by the Commissioner as the standard of comparison in determining the potency of the capreomycin working standard.

(45) *Rifampin*. The term "rifampin master standard" means a specific lot of rifampin designated by the Commissioner as the standard of comparison in determining the potency of the rifampin working standard.

(46) *Mincycline*. The term "minocycline master standard" means a specific lot of minocycline designated by the Commissioner as the standard of comparison in determining the potency of the minocycline working standard.

(47) *Spectinomycin*. The term "spectinomycin master standard" means a

specific lot of spectinomycin designated by the Commissioner in determining the standard of comparison in determining the potency of the spectinomycin working standard.

(48) *Citrandamycin palmitate hydrochloride*. The term "clindamycin palmitate hydrochloride master standard" means a specific lot of clindamycin palmitate hydrochloride designated by the Commissioner as the standard of comparison in determining the potency of the clindamycin palmitate hydrochloride working standard.

(49) *Carbenticillin indanyl*. The term "carbenticillin indanyl master standard" means a specific lot of carbenticillin indanyl designated by the Commissioner in determining the potency of the carbenticillin indanyl working standard.

(50) *Cephapirin*. The term "cephapirin master standard" means a specific lot of cephalapirin that is designated by the Commissioner as the standard of comparison in determining the potency of the cephalapirin working standard.

(51) *Cefazolin*. The term "cefazolin master standard" means a specific lot of cefazolin that is designated by the Commissioner as the standard of comparison in determining the potency of the cefazolin working standard.

(52) *Mitomycin*. The term "mitomycin master standard" means a specific lot of crystalline mitomycin that is designated by the Commissioner as the standard of comparison in determining the potency of the mitomycin working standard.

(53) *Amoxicillin*. The term "amoxicillin master standard" means a specific lot of amoxicillin that is designated by the Commissioner as the standard of comparison in determining the potency of the amoxicillin working standard.

(54) [Reserved]

(55) *Cephradine*. The term "cephradine master standard" means a specific lot of cephradine that is designated by the Commissioner as the standard of comparison in determining the potency of the cephradine working standard.

(56) *Doxorubicin*. The term "doxorubicin master standard" means a specific lot of crystalline doxorubicin that is

designated by the Commissioner as the standard of comparison in determining the potency of the doxorubicin working standard.

(57) *Bleomycin*. The term "bleomycin master standard" means a specific lot of bleomycin designated by the Commissioner as the standard of comparison in determining the potency of the bleomycin working standard.

(58) *Tobramycin*. The term "tobramycin master standard" means a specific lot of tobramycin designated by the Commissioner as the standard of comparison in determining the potency of the tobramycin working standard.

(59) *Amikacin*. The term "amikacin master standard" means a specific lot of amikacin designated by the Commissioner as the standard of comparison in determining the potency of the amikacin working standard.

(60) *Vidarabine*. The term "vidarabine master standard" means a specific lot of vidarabine that is designated by the Commissioner as the standard of comparison in determining the potency of the vidarabine working standard.

(61) *Ticarcillin*. The term "ticarcillin master standard" means a specific lot of ticarcillin designated by the Commissioner as the standard of comparison in determining the potency of the ticarcillin working standard.

(62) *Cefadroxil*. The term "cefadroxil master standard" means a specific lot of cefadroxil that is designated by the Commissioner as the standard of comparison in determining the potency of the cefadroxil working standard.

(63) *Natamycin*. The term "natamycin master standard" means a specific lot of natamycin designated by the Commissioner as the standard of comparison in determining the potency of the natamycin working standard.

(64) *Cefoxitin*. The term "cefoxitin master standard" means a specific lot of cefoxitin that is designated by the Commissioner as the standard of comparison in determining the potency of the cefoxitin working standard.

(65) *Cefamandole*. The term "cefamandole master standard" means a specific lot of cefamandole that is designated by the Commissioner as the

standard of comparison in determining the potency of the cefamandole working standard.

(66) *Cefaclor*. The term "cefaclor master standard" means a specific lot of cefaclor that is designated by the Commissioner as the standard of comparison in determining the potency of the cefaclor working standard.

(67) *Cyclacillin*. The term "cyclacillin master standard" means a specific lot of cyclacillin that is designated by the Commissioner as the standard of comparison in determining the potency of the cyclacillin working standard.

(68) *Daunorubicin*. The term "daunorubicin master standard" means a specific lot of daunorubicin that is designated by the Commissioner as the standard of comparison in determining the potency of the daunorubicin working standard.

(69) *Sisomicin*. The term "sisomicin master standard" means a specific lot of sisomicin that is designated by the Commissioner as the standard of comparison in determining the potency of the sisomicin working standard.

(70) *Meclocycline*. The term "meclocycline master standard" means a specific lot of meclocycline that is designated by the Commissioner as the standard of comparison in determining the potency of the meclocycline working standard.

(71) *Cefotaxime*. The term "cefotaxime master standard" means a specific lot of cefotaxime that is designated by the Commissioner as the standard of comparison in determining the potency of the cefotaxime working standard.

(72) *Mezlocillin*. The term "mezlocillin master standard" means a specific lot of mezlocillin that is designated by the Commissioner as the standard of comparison in determining the potency of the mezlocillin working standard.

(73) *Moxalactam*. The term "moxalactam master standard" means a specific lot of moxalactam that is designated by the Commissioner as the standard of comparison in determining the potency of the moxalactam working standard.

(74) *Piperacillin*. The term "piperacillin master standard" means a specific lot of piperacillin that is designated by the Commissioner as the standard

cific lot of a homogeneous preparation of gentamicin. The term "dactinomycin working standard" means a specific lot of a homogeneous preparation of dactinomycin.

(32) *Candicidin*. The term "candicidin working standard" means a specific lot of a homogeneous preparation of candidin.

(33) *Cephadolin*. The term "cephadolin working standard" means a specific lot of a homogeneous preparation of cephalothin.

(34) *Lincomycin*. The term "lincomycin working standard" means a specific lot of a homogeneous preparation of lincomycin.

(35) *Methacycline*. The term "methacycline working standard" means a specific lot of homogeneous preparation of methacycline.

(36) *Doxycycline*. The term "doxycycline working standard" means a specific lot of homogeneous preparation of *o*-6-deoxyxytetracycline.

(37) *Cephloridine*. The term "cephloridine working standard" means a specific lot of homogeneous preparation of cephaloridine.

(38) *Plicamycin*. The term "plicamycin working standard" means a specific lot of a homogeneous preparation of plicamycin.

(39) *Cindamycin*. The term "cindamycin working standard" means a specific lot of a homogeneous preparation of cindamycin.

(40) *Cephaloglycin*. The term "cephaloglycin working standard" means a specific lot of homogeneous preparation of cephaloglycin.

(41) *Carbenicillin*. The term "carbenicillin working standard" means a specific lot of homogeneous preparation of carbenicillin.

(42) *Cephalexin*. The term "cephalexin working standard" means a specific lot of a homogeneous preparation of cephalalexin.

(43) [Reserved]

(44) *Capreomycin*. The term "capreomycin working standard" means a specific lot of a homogeneous preparation of capreomycin.

(45) *Rifampin*. The term "rifampin working standard" means a specific lot of a homogeneous preparation of rifampin.

(46) *Minoocycline*. The term "minoocycline working standard" means a specific lot of a homogeneous preparation of minocycline.

(47) *Spectinomycin*. The term "spectinomycin working standard" means a specific lot of a homogeneous preparation of spectinomycin.

(48) *Cindamycin palmitate hydrochloride*. The term "cindamycin palmitate hydrochloride working standard" means a specific lot of a homogeneous preparation of cindamycin palmitate hydrochloride.

(49) *Carbenicillin indanyl*. The term "carbenicillin indanyl working standard" means a specific lot of a homogeneous preparation of carbenicillin indanyl.

(50) *Cephapirin*. The term "cephapirin working standard" means a specific lot of a homogeneous preparation of cephalirin.

(51) *Cefazolin*. The term "cefazolin working standard" means a specific lot of a homogeneous preparation of cefazolin.

(52) *Mitomycin*. The term "mitomycin working standard" means a specific lot of a homogeneous preparation of mitomycin.

(53) *Amoxicillin*. The term "amoxicillin working standard" means a specific lot of a homogeneous preparation of amoxicillin.

(54) [Reserved]

(55) *Cephhradine*. The term "cephhradine working standard" means a specific lot of a homogeneous preparation of cephradine.

(56) *Doxornubicin*. The term "doxornubicin working standard" means a specific lot of a homogeneous preparation of doxorubicin.

(57) *Bleomycin*. The term "bleomycin working standard" means a specific lot of a homogeneous preparation of bleomycin.

(58) *TobrAMYcin*. The term "tobramycin working standard" means a specific lot of a homogeneous preparation of tobramycin.

(59) *Amikacin*. The term "amikacin working standard" means a specific lot of a homogeneous preparation of amikacin.

(60) *Vidarabine*. The term "vidarabine working standard" means a specific lot of a homogeneous preparation of vidarabine.

cific lot of a homogeneous preparation of vidarabine.

(61) *Ticarcillin*. The term "ticarcillin working standard" means a specific lot of a homogeneous preparation of ticarcillin.

(62) *Cefadroxil*. The term "cefadroxil working standard" means a specific lot of a homogeneous preparation of cefadroxil.

(63) *Nalampicin*. The term "nalampicin working standard" means a specific lot of a homogeneous preparation of nalampicin.

(64) *Cefoxitin*. The term "cefoxitin working standard" means a specific lot of a homogeneous preparation of cefoxitin.

(65) *Cefamandole*. The term "cefamandole working standard" means a specific lot of a homogeneous preparation of cefamandole.

(66) *Cefaclor*. The term "cefaclor working standard" means a specific lot of a homogeneous preparation of cefaclor.

(67) *Cyclacillin*. The term "cyclacillin working standard" means a specific lot of a homogeneous preparation of cyclacillin.

(68) *Daurorubicin*. The term "daurorubicin working standard" means a specific lot of a homogeneous preparation of daurorubicin.

(69) *Sisomicin*. The term "sisomicin working standard" means a specific lot of a homogeneous preparation of sisomicin.

(70) *Meclocycline*. The term "meclocycline working standard" means a specific lot of a homogeneous preparation of meclocycline.

(71) *Cefotaxime*. The term "cefotaxime working standard" means a specific lot of a homogeneous preparation of cefotaxime.

(72) *Meclocillin*. The term "meclocillin working standard" means a specific lot of a homogeneous preparation of meclocillin.

(73) *Moxalactam*. The term "moxalactam working standard" means a specific lot of a homogeneous preparation of moxalactam.

(74) *Piperacillin*. The term "piperacillin working standard" means a specific lot of a homogeneous preparation of piperacillin.

(75) *Azlocillin*. The term "azlocillin working standard" means a specific lot of a homogeneous preparation of azlocillin.

(76) *Cefoperazone*. The term "cefoperazone working standard" means a specific lot of a homogeneous preparation of cefoperazone.

(77) *Netilmicin*. The term "netilmicin working standard" means a specific lot of a homogeneous preparation of netilmicin.

(78) *Cefuroxime*. The term "cefuroxime working standard" means a specific lot of a homogeneous preparation of cefuroxime.

(79) *Ceftizoxime*. The term "ceftizoxime working standard" means a specific lot of a homogeneous preparation of ceftizoxime.

(80) *4-Epitytracycline*. The term "4-epitytracycline working standard" means a specific lot of a homogeneous preparation of 4-epitytracycline.

(81) *Chloramphenicol palmitate*. The term "chloramphenicol palmitate working standard" means a specific lot of a homogeneous preparation of chloramphenicol palmitate.

(82) *Cyclosporine*. The term "cyclosporine working standard" means a specific lot of a homogeneous preparation of cyclosporine.

(83) *Ceforanide*. The term "ceforanide working standard" means a specific lot of a homogeneous preparation of ceforanide.

(84) *Cefonicid*. The term "cefonicid working standard" means a specific lot of a homogeneous preparation of cefonicid.

(85) *Clavulanic acid*. The term "clavulanic acid working standard" means a specific lot of a homogeneous preparation of clavulanic acid or a salt thereof.

(86) *Amdinocillin*. The term "amdinocillin working standard" means a specific lot of a homogeneous preparation of amdinocillin.

(87) *Ceftriaxone*. The term "ceftriaxone working standard" means a specific lot of a homogeneous preparation of ceftriaxone.

(88) *Stat. 1055-1056 as amended*. (Secs. 507, 512(n), 701 (f) and (g), 52 Stat. 1055-1056 as amended)

463 as amended, 82 Stat. 350-351 (21 U.S.C. 357, 360)(n), 371 (1) and (g))

(39 FR 18925, May 30, 1974, as amended at 39 FR 34031, Sept. 23, 1974; 39 FR 44012, Dec. 20, 1974; 40 FR 26270, June 23, 1975; 40 FR 52003, Nov. 7, 1975; 40 FR 57795; Dec. 12, 1975; 41 FR 14183, Apr. 2, 1976; 41 FR 49482, Nov. 9, 1976; 42 FR 14092, Mar. 15, 1977; 42 FR 44223, Sept. 2, 1977; 42 FR 1977; 42 FR 44223, Sept. 2, 1977; 42 FR 59854, Nov. 22, 1977; 43 FR 20976, May 16, 1978; 43 FR 41195, Sept. 15, 1978; 43 FR 1978; 43 FR 41195, Sept. 15, 1978; 43 FR 55382, Nov. 28, 1978; 44 FR 10372, Feb. 22, 1979; 44 FR 20663, Apr. 6, 1979; 45 FR 17519, Nov. 14, 1980; 46 FR 2979, 2987, Jan. 13, 1981; 46 FR 3831, 3835, Jan. 16, 1981; 46 FR 15880, Mar. 10, 1981; 46 FR 25602, 25605, May 8, 1981; 46 FR 58298, Dec. 1, 1981; 46 FR 61069, 61071, Dec. 15, 1981; 47 FR 15768, Nov. 8, 1982; 47 FR 53347, Nov. 26, 1982; 48 Apr. 13, 1982; 47 FR 53347, Nov. 26, 1982; 48 FR 789, Jan. 7, 1983; 48 FR 18800, Nov. 8, 1983; 48 FR 38459, Aug. 24, 1983; 48 FR 46270, Oct. 12, 1983; 48 FR 51290, Nov. 8, 1983; 49 FR 5096, Feb. 10, 1984; 49 FR 6091, Feb. 17, 1984; 49 FR 22631, May 31, 1984; 49 FR 25846, June 25, 1984; 49 FR 34347, 34350, Aug. 30, 1984; 49 FR 39670, Oct. 10, 1984; 50 FR 1504, Jan. 11, 1985; 50 FR 7764, Feb. 26, 1985; 50 FR 9998, Mar. 13, 1985)

§ 430.6 Definitions of the terms "unit" and "microgram" as applied to antibiotic substances.

Unless it has been otherwise specified in the individual definitions in this section, the activity assigned to each "unit" or "microgram" is equivalent to an International Unit, if such has been defined by the World Health Organization.

(a) "Unit" (1) *Penicillin*—(i) *Penicillin G*. The term "unit" applies to penicillin G means the penicillin activity (potency) contained in 0.600 microgram of the penicillin G master standard.

(ii) [Reserved]

(iii) *Penicillin V*. The term "unit" applied to penicillin V means the penicillin activity (potency) contained in 0.590 microgram of the penicillin V master standard.

(2) *Bacitracin*. The term "unit" applied to bacitracin means a bacitracin activity (potency) contained in 13.51 micrograms of the bacitracin master standard, except that when the activity (potency) of bacitracin is expressed in terms of its weight, as in the feed and drinking water of animals, 1 gram of activity is equivalent to 42,000 units.

(3) *Nystatin*. The term "unit" applied to nystatin means the nystatin activity (potency) contained in 0.2817 microgram of the nystatin master standard when dried for 2 hours at 40° C. and a pressure of 5 millimeters or less.

(4) *Polymyxin B*. The term "unit" applied to polymyxin B means the polymyxin activity (potency) contained in 0.1274 microgram of the polymyxin B master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(5) *Bleomycin*. The term "unit" applied to bleomycin means the bleomycin activity (potency) contained in 0.637 milligram of the bleomycin master standard.

(b) "Microgram"—(1) *Streptomycin*. The term "microgram" means the streptomycin activity (potency) contained in 1.250 micrograms of the streptomycin master standard after it is dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(2) *Dihydrostreptomycin*. The term "microgram" applied to dihydrostreptomycin means the dihydrostreptomycin activity (potency) contained in 1.25 micrograms of the dihydrostreptomycin master standard after it is dried for 4 hours at 100° C. and a pressure of 50 microns or less.

(3) *Chlortetracycline*. The term "microgram" applied to chlortetracycline means the chlortetracycline activity (potency) contained in 1.0 microgram of the chlortetracycline master standard.

(4) *Demeclocycline*. The term "microgram" applied to demeclocycline means the demeclocycline activity (potency) contained in 1.0 microgram of the demeclocycline master standard after it is dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(5) *Tetracycline*. The term "microgram" applied to tetracycline means the tetracycline activity (potency) contained in 1.0 microgram of the tetracycline master standard.

(6) *Rolitetraacycline*. The term "microgram" applied to rolitetraacycline means the rolitetraacycline activity (potency) contained in 1.0 microgram of the rolitetraacycline master standard

when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(7) *Chloramphenicol*. The term "microgram" applied to chloramphenicol means the chloramphenicol activity (potency) contained in 1.0 microgram of the chloramphenicol master standard.

(8) *Methicillin*. The term "microgram" applied to methicillin means the methicillin activity (potency) contained in 1.105 micrograms of the methicillin master standard.

(9) *Oxacillin*. The term "microgram" applied to oxacillin means the oxacillin activity (potency) contained in 1.111 micrograms of the oxacillin master standard.

(10) *Amphotericin*. The term "microgram" applied to amphotericin means the amphotericin activity (potency) contained in 0.9355 microgram of the amphotericin master standard when dried for 4 hours at 60° C. and a pressure of 5 millimeters or less.

(11) *Amphotericin A*. The term "microgram" applied to amphotericin A means the amphotericin A activity (potency) contained in 1.0 microgram of the amphotericin A master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(12) *Amphotericin B*. The term "microgram" applied to amphotericin B means the amphotericin B activity (potency) contained in 1.014 micrograms of the amphotericin B master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(13) *Colistin*. The term "microgram" applied to colistin means the colistin base activity (potency) contained in 1.495 micrograms of the colistin master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less. The numerical value of a microgram of colistin is not equivalent to the International Unit.

(14) *Colistimethate*. The term "microgram" applied to colistimethate means the activity (potency) calculated as colistin base that is contained in 1.938 micrograms of the colistimethate master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less. The numerical value of a microgram of colistimethate is not equivalent to the International Unit.

(15) *Cycloserine*. The term "microgram" applied to cycloserine means the cycloserine activity (potency) contained in 1.0 microgram of the cycloserine master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(16) *Erythromycin*. The term "microgram" applied to erythromycin means the erythromycin base activity (potency) contained in 1.02 micrograms of the erythromycin master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(17) *Gramicidin*. The term "microgram" applied to gramicidin means the gramicidin activity (potency) contained in 1.0 microgram of the gramicidin master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(18) *Griseofulvin*. The term "microgram" applied to griseofulvin means the griseofulvin activity (potency) contained in 1.0 microgram of the griseofulvin master standard.

(19) *Kanamycin*. The term "microgram" applied to kanamycin means the kanamycin base activity (potency) contained in 1.269 micrograms of the kanamycin master standard.

(20) *Neomycin*. The term "microgram" applied to neomycin means the neomycin base activity (potency) contained in 1.429 micrograms of the neomycin master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(21) *Novobiocin*. The term "microgram" applied to novobiocin means the novobiocin acid activity (potency) contained in 1.033 micrograms of the novobiocin master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(22) *Oleandomycin*. The term "microgram" applied to oleandomycin means the oleandomycin base activity (potency) contained in 1.176 micrograms of the oleandomycin master standard.

(23) *Troleandomycin*. The term "microgram" applied to troleandomycin means the activity (potency) calculated as the molecular equivalent of the oleandomycin base, contained in 1.2315 micrograms of the troleandomycin master standard.

(24) *Oxytetracycline*. The "microgram" applied to oxytetracycline means the oxytetracycline base activity (potency) contained in 1.13 micrograms of the oxytetracycline master standard.

(25) *Paromomycin*. The term "microgram" applied to paromomycin means the paromomycin activity (potency) contained in 1.333 micrograms of the paromomycin master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(26) *Tyrosin*. The term "microgram" applied to tyrosin means the activity (potency) contained in 0.2 microgram of the granulin master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(27) *Vancomycin*. The term "microgram" applied to vancomycin means the vancomycin base activity (potency) contained in 1.25 micrograms of the vancomycin master standard.

(28) [Reserved]

(29) *Ampicillin*. The term "microgram" applied to ampicillin means the ampicillin activity (potency) contained in 1.1764 micrograms of the ampicillin master standard.

(30) *Nafcillin*. The term "microgram" applied to nafcillin means the nafcillin activity (potency) contained in 1.0989 micrograms of the nafcillin master standard.

(31) *Gentamicin*. The term "microgram" applied to gentamicin means the gentamicin activity (potency) contained in 1.56 micrograms of the gentamicin master standard when dried for 3 hours at 110° C. and a pressure of 5 millimeters or less.

(32) *Dactinomycin*. The term "microgram" applied to dactinomycin means the dactinomycin activity (potency) contained in 1.000 microgram of the dactinomycin master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(33) *Candidin*. The term "microgram" applied to candidin means the candidin activity (potency) contained in 1.0 microgram of the candidin master standard when dried for 3 hours at 40° C. and a pressure of 5 millimeters or less.

(34) *Cephalothin*. The term "microgram" applied to cephalothin means

the cephalothin activity (potency) contained in 1.066 micrograms of the cephalothin master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(35) *Lincomycin*. The term "microgram" applied to lincomycin means the lincomycin base activity (potency) contained in 1.156 micrograms of the lincomycin master standard.

(36) *Cloxacillin*. The term "microgram" applied to cloxacillin means the cloxacillin activity (potency) contained in 1.135 micrograms of the cloxacillin master standard.

(37) *Methacycline*. The term "microgram" applied to methacycline means the methacycline activity (potency) contained in 1.082 micrograms of the methacycline master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(38) *Doxycycline*. The term "microgram" applied to doxycycline means the doxycycline activity (potency) contained in 1.155 micrograms of the doxycycline master standard.

(39) *Cephaloridine*. The term "microgram" applied to cephaloridine means the cephaloridine activity (potency) contained in 1.00806 micrograms of the cephaloridine master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(40) *Dicloxacillin*. The term "microgram" applied to dicloxacillin means the dicloxacillin activity (potency) contained in 1.087 micrograms of the dicloxacillin master standard.

(41) *Plicamycin*. The term "microgram" applied to plicamycin means the plicamycin activity (potency) contained in 1.000 microgram of the plicamycin master standard when dried for 4 hours at 25° C. and a pressure of 5 millimeters or less.

(42) *Cindamycin*. The term "microgram" applied to cindamycin means the cindamycin activity (potency) contained in 1.139 micrograms of the cindamycin master standard.

(43) *Cephaloglycin*. The term "microgram" applied to cephaloglycin means the cephaloglycin activity (potency) contained in 1.02564 micrograms of the cephaloglycin master standard.

(44) *Carbenicillin*. The term "microgram" applied to carbenicillin means the carbenicillin activity (potency) contained in 1.135 micrograms of the carbenicillin master standard.

(45) *Cephalexin*. The term "microgram" applied to cephalexin means the cephalexin activity (potency) contained in 1.0707 micrograms of the cephalexin master standard.

(46) [Reserved]

(47) *Capreomycin*. The term "microgram" applied to capreomycin means the capreomycin activity (potency) contained in 1.0870 micrograms of the capreomycin master standard when dried for 4 hours at 100° C. and a pressure of 5 millimeters or less.

(48) *Rifampin*. The term "microgram" applied to rifampin means the rifampin activity (potency) contained in 1.0101 micrograms of the rifampin master standard.

(49) *Minoocycline*. The term "microgram" applied to minocycline means the minocycline activity (potency) contained in 1.1588 micrograms of the minocycline master standard.

(50) *Spectinomycin*. The term "microgram" applied to spectinomycin means the spectinomycin activity (potency) contained in 1.490 micrograms of the spectinomycin master standard.

(51) *Cindamycin palmitate hydrochloride*. The term "microgram" applied to cindamycin palmitate hydrochloride means the cindamycin activity (potency) contained in 1.661 micrograms of the cindamycin palmitate hydrochloride master standard.

(52) *Carbenicillin indanyl*. The term "microgram" applied to carbenicillin indanyl means the carbenicillin activity (potency) contained in 1.4514 micrograms of the carbenicillin indanyl master standard.

(53) *Cephapirin*. The term "microgram" applied to cephalapirin means the cephalapirin activity (potency) contained in 1.0616 micrograms of the cephalapirin master standard.

(54) *Cefazolin*. The term "microgram" applied to cefazolin means the cefazolin activity (potency) contained in 1.005 micrograms of the cefazolin master standard.

(55) *Mitomycin*. The term "microgram" applied to mitomycin means the mitomycin activity (potency) con-

tained in 1.0416 micrograms of the mitomycin master standard.

(56) *Amoxicillin*. The term "microgram" applied to amoxicillin means the amoxicillin activity (potency) contained in 1.17647 micrograms of the amoxicillin master standard.

(57) [Reserved]

(58) *Cephradine*. The term "microgram" applied to cephradine means the cephradine activity (potency) contained in 1.1111 micrograms of the cephradine master standard.

(59) *Doxorubicin*. The term "microgram" applied to doxorubicin means the activity (potency) calculated as doxorubicin hydrochloride contained in 1.0204 micrograms of the doxorubicin master standard.

(60) *Tobramycin*. The term "microgram" applied to tobramycin means the tobramycin activity (potency) contained in 1.126 micrograms of the tobramycin master standard.

(61) *Amikacin*. The term "microgram" applied to amikacin means the amikacin activity (potency) contained in 1.091 micrograms of the amikacin master standard.

(62) *Vidarabine*. The term "microgram" applied to vidarabine means the vidarabine activity (potency) contained in 1.0674 micrograms of the vidarabine master standard.

(63) *Ticarcillin*. The term "microgram" applied to ticarcillin means the ticarcillin activity (potency) contained in 1.136 micrograms of the ticarcillin master standard.

(64) *Cefadroxi*. The term "microgram" applied to cefadroxi means the cefadroxi activity (potency) contained in 1.0537 micrograms of the cefadroxi master standard.

(65) *Natamycin*. The term "microgram" applied to natamycin means the natamycin activity (potency) contained in 1.0846 micrograms of the natamycin master standard.

(66) *Cefoxitin*. The term "microgram" applied to cefoxitin means the cefoxitin activity (potency) contained in 1.072 micrograms of the cefoxitin master standard.

(67) *Cefamandole*. The term "microgram" applied to cefamandole means the cefamandole activity (potency) contained in 1.1364 micrograms of the cefamandole master standard.

applied to cefaclor means the cefaclor activity (potency) contained in 1.0493 micrograms of cefaclor master standard.

(69) *Cyclacillin*. The term "microgram" applied to cyclacillin means the cyclacillin activity (potency) contained in 1.01 micrograms of the cyclacillin master standard.

(70) *Daunorubicin*. The term "microgram" applied to daunorubicin means the daunorubicin activity (potency) contained in 1.0965 micrograms of the daunorubicin master standard.

(71) *Sisomicin*. The term "microgram" applied to sisomicin means the sisomicin activity (potency) contained in 1.00 microgram of the sisomicin master standard expressed on an anhydrous basis.

(72) *Meclocycline*. The term "microgram" applied to meclocycline means the meclocycline activity (potency) contained in 1.0493 micrograms of the meclocycline master standard.

(73) *Cefotaxime*. The term "microgram" applied to cefotaxime means the cefotaxime activity (potency) contained in 1.089 micrograms of cefotaxime master standard.

(74) *Mezlocillin*. The term "microgram" applied to mezlocillin means the mezlocillin activity (potency) contained in 1.1086 micrograms of the mezlocillin master standard.

(75) *Moxalactam*. The term "microgram" applied to moxalactam means the moxalactam activity (potency) contained in 1.1173 micrograms of the moxalactam master standard.

(76) *Piperacillin*. The term "microgram" applied to piperacillin means the piperacillin activity (potency) contained in 1.0460 micrograms of the piperacillin master standard.

(77) *Cefoperazone*. The term "microgram" applied to cefoperazone means the cefoperazone activity (potency) contained in 1.056 micrograms of the cefoperazone master standard.

(78) *Azlocillin*. The term "microgram" applied to azlocillin means the azlocillin activity (potency) contained in 1.128 micrograms of the azlocillin master standard.

(79) *Netilmicin*. The term "microgram" applied to netilmicin means the netilmicin activity (potency) contained

master standard expressed on an anhydrous basis.

(80) *Cefuroxime*. The term "microgram" applied to cefuroxime means the cefuroxime activity (potency) contained in 1.0893 micrograms of the cefuroxime master standard.

(81) *Ceftizoxime*. The term "microgram" applied to ceftizoxime means the ceftizoxime activity (potency) contained in 1.011 micrograms of the ceftizoxime master standard.

(82) *Cyclosporine*. The term "microgram" applied to cyclosporine means the cyclosporine activity (potency) contained in 1.0173 micrograms of cyclosporine master standard.

(83) *Ceforanide*. The term "microgram" applied to ceforanide means the ceforanide activity (potency) contained in 1.005 micrograms of the ceforanide master standard.

(84) *Cefonid*. The term "microgram" applied to cefonid means the cefonid activity (potency) contained in 1.150 micrograms of the cefonid master standard.

(85) *Clavulanic acid*. The term "microgram" applied to clavulanic acid means the clavulanic acid activity (potency) contained in 1.053 micrograms of clavulanic acid master standard.

(86) *Amdinocillin*. The term "microgram" applied to amdinocillin means the amdinocillin activity (potency) contained in 1.004 micrograms of the amdinocillin master standard.

(87) *Ceftriaxone*. The term "microgram" applied to ceftriaxone means the ceftriaxone activity (potency) contained in 1.19 micrograms of the ceftriaxone master standard.

(Sees. 507, 701 (f) and (g), 52 Stat. 1055-1056, 59 Stat. 463 as amended (21 U.S.C. 357, 371 (f) and (g)))

139 FR 18925, May 30, 1974, as amended at 39 FR 34031, Sept. 23, 1974, 39 FR 44012, Dec. 12, 1974; 40 FR 26270, June 23, 1975; 40 FR 52003, Nov. 7, 1975; 40 FR 57797, Dec. 12, 1975; 41 FR 14183, Apr. 2, 1976; 41 FR 44381, Oct. 8, 1976; 41 FR 44483, Nov. 9, 1976; 42 FR 14092, Mar. 15, 1977; 42 FR 44223, Sept. 2, 1977; 42 FR 59854, Nov. 22, 1977; 43 FR 20976, May 16, 1978; 43 FR 55382, Nov. 28, 1978; 44 FR 10372, Feb. 20, 1979; 44 FR 20663, Apr. 6, 1979; 45 FR 75194, Nov. 14, 1980; 46 FR 2979, 2987, Jan. 13, 1981; 46 FR 3831, 3835, Jan. 16, 1981; 46 FR 28605, May 8, 1981; 46 FR 58298, Dec. 1,

1981; 47 FR 15768, Apr. 13, 1982; 47 FR 33493, Aug. 3, 1982; 47 FR 53348, Nov. 26, 1982; 48 FR 789, Jan. 7, 1983; 48 FR 18800, Apr. 26, 1983; 48 FR 24062, May 31, 1983; 48 FR 38460, Aug. 24, 1983; 48 FR 46270, Oct. 12, 1983; 49 FR 5096, Feb. 10, 1984; 49 FR 22631, May 31, 1984; 49 FR 28846, June 25, 1984; 49 FR 34347, 34350, Aug. 30, 1984; 49 FR 39670, Oct. 10, 1984; 50 FR 1504, Jan. 11, 1985; 50 FR 7764, Feb. 26, 1985; 50 FR 9999, Mar. 13, 1985)

Subpart B—Antibiotic Drugs Affected by the Drug Amendments of 1962

§ 430.10 Certification or release of antibiotic drugs affected by the drug amendments of 1962.

(a) Before the 1962 amendments to the Federal Food, Drug, and Cosmetic Act only permitted the Food and Drug Administration to provide for the certification of batches of antibiotic drugs containing penicillin, streptomycin, chlorotetracycline, chloramphenicol, or bacitracin, or any derivative of them. FDA certified those drugs under regulations promulgated on the basis of scientific proof of the drugs' safety and effectiveness. Most drugs containing an antibiotic other than one of those listed were subject to the new drug provisions of the act, which required that an applicant show that the drug was safe and obtain FDA approval of a new drug application before marketing it. An affirmative showing of effectiveness was not then required to obtain approval. Some antibiotic drugs that were not subject to certification, however, were also not subject to the new drug provisions of the act under informal FDA opinions that the drug was "not a new drug" or "no longer a new drug." FDA revoked those opinions under § 310.100 of this chapter.

(b) The 1962 amendments amended section 507 of the act to require the certification, release without certification, or exemption from certification, of all antibiotic drugs on the basis of scientific proof of safety and effectiveness. The amendments provided that FDA implement them for antibiotic drugs that were marketed on April 30, 1963 and were not subject to the certification provisions on that date. FDA is implementing the amendments with

respect to antibiotic drugs for which the act through its Drug Efficacy Study Implementation (DESI) program under which the agency is evaluating those antibiotic drugs for efficacy. Until FDA completes that evaluation it will permit continued marketing of those antibiotic drugs under paragraph (c) of this section. The agency is also implementing the 1962 amendments with respect to antibiotic drugs formerly not subject to either the certification or new drug provisions of the act and the agency is evaluating those antibiotic drugs for both safety and efficacy. Until FDA completes that evaluation, it will permit continued marketing of those antibiotic drugs under paragraph (d) of this section.

(c) Unless exempted from certification, FDA will certify or release antibiotic drugs which on April 30, 1963 were the subject of an approved new drug application under section 505 of the act, under regulations providing for certification of the drugs. Although the initial regulation for each of these drugs established under section 507(h) of the act was not conditioned upon an affirmative finding of the effectiveness of the drug, FDA is proceeding under its DESI program to amend or repeal those regulations to provide for certification of those drugs only if they had been shown to be both safe and effective.

(d) Unless exempted from certification, FDA will release without certification an antibiotic drug that was marketed on April 30, 1963, but not subject to certification, and not subject to an approved new drug application on that date, unless FDA has made a determination that the drug has not been shown to be safe or lacks substantial evidence of effectiveness under the DESI program. FDA is proceeding under its DESI program to establish regulations under section 507 to provide for certification of those drugs only if they have been shown to be safe and effective.

(Sees. 409, 501, 502, 503, 505, 506, 507, 512-516, 520, 701, 706, 52 Stat. 1049-1053 as amended, 1055, 1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended, 72 Stat. 1788-1788 as amended, 74 Stat. 399-407 as amend-

Sec. **Subpart C—Administrative Procedures**

430.20 Procedure for the issuance, amendment, or repeal of regulations.

ATTORNEY: Secs. 507, 701(a), 59 Stat. 463, as amended, 52 Stat. 1055 (21 U.S.C. 357, 371(a)), unless otherwise noted.

SOURCE: 39 FR 18925, May 30, 1974, unless otherwise noted.

Subpart A—General Provisions

§ 430.3 Definitions applicable to all certifiable antibiotic drugs.

(a) The definitions and interpretations contained in section 201 of the Federal Food, Drug, and Cosmetic Act shall be applicable to such terms when used in the regulations in this chapter covering the certification of antibiotic and antibiotic-containing drugs.

(b) The term "Commissioner" means the Commissioner of Food and Drugs and any other officer of the Food and Drug Administration whom he may designate to act in his behalf for the purpose of the regulations for the certification of antibiotic and antibiotic-containing drugs.

(c) The term "act" means the Federal Food, Drug, and Cosmetic Act and amendments thereto. (52 Stat. 1040 et seq.; 21 U.S.C. 301-392).

(d) The term "U.S.P." means the official Pharmacopeia of the United States, including supplements thereto. The term "N.F." means the official National Formulary, including supplements thereto.

(e) The term "batch" means a specific homogeneous quantity of a drug.

(f) The term "batch mark" means an identifying mark or other identifying device assigned to a batch by the manufacturer or packer thereof.

(g) The term "manufacture" does not include the use of a drug as an ingredient in compounding any prescription issued by a practitioner licensed by law to administer such drug.

§ 430.4 Definitions of antibiotic substances.

(a) The following are definitions of antibiotic substances:

(1) *Penicillin*. Each of the several antibiotic substances (e.g., penicillin F, penicillin G, penicillin X) produced by

the growth of *Penicillium notatum* or *Penicillium chrysogenum*, and each of the same substances produced by any other means, is a kind of penicillin.

(2) *Streptomycin*. Each of the several antibiotic substances produced by the growth of *Streptomyces griseus*, and each of the same substances produced by any other means, is a kind of streptomycin.

(3) *Dihydrostreptomycin*. Each of the antibiotic substances produced by hydrogenation of streptomycin, and each of the same substances produced by any other means, is a kind of dihydrostreptomycin.

(4) *Chlortetracycline*. Each of the several antibiotic substances produced by the growth of *Streptomyces aureofaciens*, and each of the same substances produced by any other means is a kind of chlortetracycline.

(5) *Tetracycline*. Each of the several antibiotic substances produced by the hydrogenation of chlortetracycline, and each of the same substances produced by any other means, is a kind of tetracycline.

(6) *Chloramphenicol*. Each of the several antibiotic substances produced by the growth of *Streptomyces venezuelae*, and each of the same substances produced by any other means, is a kind of chloramphenicol.

(7) *Bacitracin*. Each of the several antibiotic substances produced by the growth of *Bacillus subtilis* var. Tracy, and each of the same substances produced by any other means, is a kind of bacitracin.

(8) *Ampicillin*. Each of the antibiotic substances produced by the growth of *Streptomyces canis*, and each of the same substances produced by any other means, is a kind of ampicillin.

(9) *Ampicillin*. Each of the antibiotic substances produced by the growth of *Streptomyces nodosus*, and each of the same substances produced by any other means, is a kind of ampicillin.

(10) *Colistin*. Each of the antibiotic substances produced by the growth of *Bacillus polymyxa* var. *colistinus*, and each of the same substances produced by any other means, is a kind of colistin.

(11) *Cycloserine*. Each of the antibiotic substances produced by the growth of *Streptomyces orchidaceus*, and each of the same substances produced by any other means, is a kind of cycloserine.

(12) *Erythromycin*. Each of the antibiotic substances produced by the growth of *Streptomyces erythraeus*, and each of the same substances produced by any other means, is a kind of erythromycin.

(13) *Gramicidin*. Each of the antibiotic substances produced by the growth of *Bacillus brevis*, and each of the same substances produced by any other means, is a kind of gramicidin.

(14) *Griseofulvin*. Each of the antibiotic substances produced by the growth of *Penicillium patulum* or *Penicillium griseofulvum*, and each of the same substances produced by any other means, is a kind of griseofulvin.

(15) *Kanamycin*. Each of the antibiotic substances produced by the growth of *Streptomyces kanamyceticus*, and each of the same substances produced by any other means, is a kind of kanamycin.

(16) *Neomycin*. Each of the antibiotic substances produced by the growth of *Streptomyces fradiae*, and each of the same substances produced by any other means, is a kind of neomycin.

(17) *Novobiocin*. Each of the antibiotic substances produced by the growth of *Streptomyces niveus* (known also as *Streptomyces spheroides*), and each of the same substances produced by any other means, is a kind of novobiocin.

(18) *Nystatin*. Each of the antibiotic substances produced by the growth of *Streptomyces noursei*, and each of the same substances produced by any other means, is a kind of nystatin.

(19) *Oleandomycin*. Each of the antibiotic substances produced by the growth of *Streptomyces antibioticus*, and each of the same substances produced by any other means, is a kind of oleandomycin.

(20) *Troleandomycin*. Each of the antibiotic substances produced by the tricyclization of oleandomycin, and each of the same substances produced by any other means, is a kind of troleandomycin.

(21) *Oxytetracycline*. Each of the antibiotic substances produced by the growth of *Streptomyces rimosus*, and each of the same substances produced by any other means, is a kind of oxytetracycline.

(22) *Paromomycin*. Each of the antibiotic substances produced by the growth of *Streptomyces rimosus* var. *paromomycinus*, and each of the same substances produced by any other means, is a kind of paromomycin.

(23) *Polymyxin*. Each of the antibiotic substances produced by the growth of *Bacillus polymyxa*, and each of the same substances produced by any other means, is a kind of polymyxin.

(24) *Pivacemycin*. Each of the antibiotic substances produced by the growth of a variant of *Streptomyces plicatus*, and each of the same substances produced by any other means, is a kind of pivacemycin.

(25) *Tyrothricin*. Each of the mixtures of antibiotic substances produced by the growth of *Bacillus brevis*, and each of the same mixtures of substances produced by any other means, is a kind of tyrothricin.

(26) *Vancomycin*. Each of the antibiotic substances produced by the growth of *Streptomyces orientalis*, and each of the same substances produced by any other means, is a kind of vancomycin.

(27) [Reserved]

(28) *Gentamicin*. Each of the antibiotic substances produced by the growth of *Micromonospora purpurea*, and each of the same substances produced by any other means, is a kind of gentamicin.

(29) *Dactinomycin*. Dactinomycin is a specific kind of actinomycin produced by the growth of *Streptomyces parvulus* or the same antibiotic produced by any other means.

(30) *Candidin*. Each of the hepataene antibiotic substances produced by the growth of *Streptomyces griseus* and each of the same substances produced by any other means is a kind of candidin.

(31) *Cephalosporin*. Each of the antibiotic substances produced by the growth of *Cephalosporium acremonium*, and each of the same substances

produced by any other means, is a kind of cephalosporin.

(32) *Lincomycin*. Each of the antibiotic substances produced by the growth of *Streptomyces lincolnensis* var. *lincolnensis*, and each of the same substances produced by any other means, is a kind of lincomycin.

(33) *Demeclocycline*. Each of the antibiotic substances produced by removal of the 6-methyl group from chlorotetracycline, and each of the same substances produced by any other means, is a kind of demeclocycline.

(34) *Citrandamycin*. Each of the antibiotic substances produced by the chloro-substitution of the 7-chloro-hydroxyl group of lincomycin, and each of the same substances produced by any other means, is a kind of citrandamycin.

(35) [Reserved]

(36) *Capreomycin*. Each of the antibiotic substances produced by the growth of *Streptomyces capreolus*, and each of the same substances produced by any other means, is a kind of capreomycin.

(37) *Rifamycin*. Each of the several antibiotic substances (e.g., rifamycin A, rifamycin B, rifamycin SV) produced by the growth of *Streptomyces mediterranei*, and each of the same substances produced by any other means, is a kind of rifamycin.

(38) *Spectinomycin*. Each of the antibiotic substances produced by the growth of *Streptomyces spectabilis*, and each of the same substances produced by any other means, is a kind of spectinomycin.

(39) *Mitomycin*. Mitomycin is the antibiotic substance produced by the growth of *Streptomyces caespitosus*, and each of the same substances produced by any other means is a kind of mitomycin.

(40) *Doxorubicin*. Each of the antibiotic substances produced by the growth of *Streptomyces peuceletius* var. *caesiatus*, and each of the same substances produced by any other means, is a kind of doxorubicin.

(41) *Bleomycin*. Each of the antibiotic substances produced by the growth of *Streptomyces verticillus* and each of the same substances produced by any other means is a kind of bleomycin.

(42) *Tobramycin*. A specific one of the antibiotic substances produced by the growth of *Streptomyces tobramycinus*, and the same substance produced by any other means, is tobramycin.

(43) *Amikacin*. Each of the antibiotic substances produced by the acylation of the 1-amino group of the 2-deoxy-streptamine moiety of kanamycin A with L-(+)- γ -amino- α -hydroxybutyric acid, and each of the same substances produced by any other means is a kind of amikacin.

(44) *Vidarabine*. Vidarabine is a purine glycoside antibiotic substance produced by the growth of *Streptomyces antibioticus*, and each of the same substances produced by any other means is a kind of vidarabine.

(45) *Nalamyacin*. Each of the antibiotic substances produced by the growth of *Streptomyces natalensis*, and each of the same substances produced by any other means, is a kind of nalamyacin.

(46) *Daunorubicin*. Each of the antibiotic substances produced by the growth of *Streptomyces coerulescens* and each of the same substances produced by any other means is a kind of daunorubicin.

(47) *Sisomicin*. A specific one of the antibiotic substances produced by the growth of *Micromonospora inyoensis*, and the same substance produced by any other means, is a kind of sisomicin.

(48) *Mazalactam*. 5-Oxa-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[carboxy(4-hydroxyphenyl)acetyl]-amino]-7-methoxy-3-[[1-methyl-1H-tetrazol-5-yl]thio]-methyl]-8-oxo-, disodium salt.

(49) *Cefoperazone*. Cefoperazone is a semi-synthetic antibiotic substance produced by the acylation of the amino group at the 7 position of 7-aminocephalosporanic acid with α -(4-aminoethyl)-2,3-dioxo-1-ethyl-2,3-dioxo-1-piperazinecarboxamido)- α -(4-hydroxyphenyl) acetic acid and introduction of a methylthio-tetrazol group at the 3 position.

(50) *Netilmicin*. Netilmicin is a semi-synthetic antibiotic of the aminoglycoside group derived from sisomicin, and each of the same substances produced by any other means is a kind of netilmicin. It is D-Streptamine, 4-O-13-

amino-6-(β -aminomethyl)-3- β -D-glucaro-2H-pyran-2-yl]-2-deoxy-6-O-[3-deoxy-4-C-methyl-3-(methylamino)- β -D-arabinopyranosyl]-N'-ethyl-, (2S-cis)-

(51) *Cyclosporine*. Cyclosporine is a specific cyclic polypeptide consisting of 11 amino acids produced by the growth of *Cylindrocarpum lucidum* Booth or *Tolypocladium inflatum* Gams.

(52) *Cefonicid*. 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[(hydroxyphenylacetyl)amino]-8-oxo-3-[[1-(sulfomethyl)-1H-tetrazol-5-yl]thio]methyl]-, disodium salt, [6R-[6a7(R)R']].

(53) *Clavulanic acid*. Clavulanic acid is an antibiotic substance produced by the growth of *Streptomyces clavuligerus* having the structure described as follows: 2-(α -2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, and each of the same substances produced by any other means, is a kind of clavulanic acid.

(54) *Ceftriaxone*. Ceftriaxone is a semi-synthetic antibiotic substance produced by the addition of S-2-benzothiazolyl-2-(2-aminothiazol-4-yl)-2-methoxyiminothioacetate to the 7-amino group of 7-amino-3-(2,5-dihydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl)-thiomethyl-3-cephem-4-carboxylic acid.

(Secs. 507, 701(f) and (g), 52 Stat. 1055-1056 as amended, 59 Stat. 463 as amended (21 U.S.C. 357, 371 (f) and (g)))

(39 FR 18925, May 30, 1974, as amended at 40 FR 52003, Nov. 7, 1975; 40 FR 57796, Dec. 12, 1975; 41 FR 14183, Apr. 2, 1976; 41 FR 49482, Nov. 9, 1976; 42 FR 44223, Sept. 2, 1977; 43 FR 55382, Nov. 28, 1978; 45 FR 75194, Nov. 14, 1980; 46 FR 2867, Jan. 13, 1981; 46 FR 61069, 61071, Dec. 15, 1981; 48 FR 769, Jan. 7, 1983; 48 FR 18800, Apr. 26, 1983; 49 FR 5096, Feb. 10, 1984; 49 FR 22651, May 31, 1984; 49 FR 39670, Oct. 10, 1984; 49 FR 44460, Nov. 7, 1984; 50 FR 1504, Jan. 11, 1985; 50 FR 9998, Mar. 13, 1985)

§ 430.5 Definitions of master and working standards.

(a) *Master standards*—(1) *Penicillin*. and salts of *penicillin*—(1) *Penicillin G*. The term "penicillin G master standard" means a specific lot of crystalline penicillin G that is designated by the Commissioner as the standard of comparison for penicillin G.

Penicillin III containing one potency of the penicillin G working standard.

(ii) [Reserved]

(iii) *Penicillin V*. The term "penicillin V master standard" means a specific lot of crystalline penicillin V that is designated by the Commissioner as the standard of comparison in determining the potency of the penicillin V working standard.

(iv)—(v) [Reserved]

(vi) *Methicillin*. The term "methicillin master standard" means a specific lot of crystalline methicillin that is designated by the Commissioner as the standard of comparison in determining the potency of the methicillin working standard.

(vii) *Oxacillin*. The term "oxacillin master standard" means a specific lot of crystalline oxacillin that is designated by the Commissioner as the standard of comparison in determining the potency of the oxacillin working standard.

(viii) *Ampicillin*. The term "ampicillin master standard" means a specific lot of crystalline ampicillin that is designated by the Commissioner as the standard of comparison in determining the potency of the ampicillin working standard.

(ix) *Nafcillin*. The term "nafcillin master standard" means a specific lot of crystalline nafcillin that is designated by the Commissioner as the standard of comparison in determining the potency of the nafcillin working standard.

(x) *Cloxacillin*. The term "cloxacillin master standard" means a specific lot of crystalline cloxacillin that is designated as the standard of comparison in determining the potency of the cloxacillin working standard.

(xi) *Dicloxacillin*. The term "dicloxacillin master standard" means a specific lot of dicloxacillin that is designated by the Commissioner as the standard of comparison in determining the potency of the dicloxacillin working standard.

(xii) The term "netaillin working standard" means a specific lot of homogeneous preparation of netaillin.

(2) *Streptomycin*. The term "streptomycin master standard" means a specific lot of streptomycin that is designated by the Commissioner as the

standard of comparison in determining the potency of the streptomycin working standard.

(3) *Dihydrostreptomycin*. The term "dihydrostreptomycin master standard" means a specific lot of crystalline dihydrostreptomycin that is designated by the Commissioner as the standard of comparison in determining the potency of the dihydrostreptomycin working standard.

(4) *Chlortetracycline*. The term "chlortetracycline master standard" means a specific lot of crystalline chlortetracycline hydrochloride that is designated by the Commissioner as the standard of comparison in determining the potency of the chlortetracycline working standard.

(5) *Demeclocycline*. The term "demeclocycline master standard" means a specific lot of crystalline demeclocycline hydrochloride that is designated by the Commissioner as the standard of comparison in determining the potency of the demeclocycline working standard.

(6) *Tetracycline*. The term "tetracycline master standard" means a specific lot of crystalline tetracycline hydrochloride that is designated by the Commissioner as the standard of comparison in determining the potency of the tetracycline working standard.

(7) *Rolitetraycline*. The term "rolitetraycline master standard" means a specific lot of crystalline rolitetraycline that is designated by the Commissioner as the standard of comparison in determining the potency of the rolitetraycline working standard.

(8) *Chloramphenicol*. The term "chloramphenicol master standard" means a specific lot of crystalline chloramphenicol that is designated by the Commissioner as the standard of comparison in determining the potency of the chloramphenicol working standard.

(9) *Bactracin*. The term "bactracin master standard" means a specific lot of bactracin that is designated by the Commissioner as the standard of comparison in determining the potency of the bactracin working standard.

(10) *Amphoterycin*. The term "amphoterycin master standard" means a specific lot of amphoterycin designated by the Commissioner as the standard

of comparison in determining the potency of the amphoterycin working standard.

(11) *Amphotericin*. The term "amphotericin A master standard" means a specific lot of amphotericin A designated by the Commissioner as the standard of comparison in determining the potency of the amphotericin A working standard. The term "amphotericin B master standard" means a specific lot of amphotericin B designated by the Commissioner as the standard of comparison in determining the potency of the amphotericin B working standard.

(12) *Colistin*. The term "colistin master standard" means a specific lot of colistin designated by the Commissioner as the standard of comparison in determining the potency of the colistin working standard.

(13) *Colistimethate*. The term "colistimethate master standard" means a specific lot of colistimethate designated by the Commissioner as the standard of comparison in determining the potency of the colistimethate working standard.

(14) *Cycloserine*. The term "cycloserine master standard" means a specific lot of cycloserine designated by the Commissioner as the standard of comparison in determining the potency of the cycloserine working standard.

(15) *Erythromycin*. The term "erythromycin master standard" means a specific lot of erythromycin designated by the Commissioner as the standard of comparison in determining the potency of the erythromycin working standard.

(16) *Gramicidin*. The term "gramicidin master standard" means a specific lot of gramicidin designated by the Commissioner as the standard of comparison in determining the potency of the gramicidin working standard.

(17) *Griseofulvin*. The term "griseofulvin master standard" means a specific lot of griseofulvin designated by the Commissioner as the standard of comparison in determining the potency of the griseofulvin working standard.

(18) *Kanamycin*. The term "kanamycin master standard" means a specific lot of kanamycin designated by the Commissioner as the standard of

comparison in determining the potency of the kanamycin working standard.

(19) *Neomycin*. The term "neomycin master standard" means a specific lot of neomycin designated by the Commissioner as the standard of comparison in determining the potency of the neomycin working standard.

(20) *Novobiocin*. The term "novobiocin master standard" means a specific lot of novobiocin designated by the Commissioner as the standard of comparison in determining the potency of the novobiocin working standard.

(21) *Nystatin*. The term "nystatin master standard" means a specific lot of nystatin designated by the Commissioner as the standard of comparison in determining the potency of the nystatin working standard.

(22) *Oleandomycin*. The term "oleandomycin master standard" means a specific lot of oleandomycin designated by the Commissioner as the standard of comparison in determining the potency of the oleandomycin working standard.

(23) *Oxytetracycline*. The term "oxytetracycline master standard" means a specific lot of oxytetracycline designated by the Commissioner as the standard of comparison in determining the potency of the oxytetracycline working standard.

(24) *Paromomycin*. The term "paromomycin master standard" means a specific lot of paromomycin designated by the Commissioner as the standard of comparison in determining the potency of the paromomycin working standard.

(25) *Polymyxin B*. The term "polymyxin B master standard" means a specific lot of polymyxin B designated by the Commissioner as the standard of comparison in determining the potency of the polymyxin B working standard.

(26) [Reserved]

(27) *Vancomycin*. The term "vancomycin master standard" means a specific lot of vancomycin designated by the Commissioner as the standard of comparison in determining the potency of the vancomycin working standard.

(28) [Reserved]

(29) *Troleandomycin*. The term "troleandomycin master standard" means a specific lot of troleandomycin designated by the Commissioner as the standard of comparison in determining the potency of the troleandomycin working standard.

(30) *Gentamicin*. The term "gentamicin master standard" means a specific lot of gentamicin designated by the Commissioner as the standard of comparison in determining the potency of the gentamicin working standard.

(31) *Dactinomycin*. The term "dactinomycin master standard" means a specific lot of dactinomycin designated by the Commissioner as the standard of comparison in determining the potency of the dactinomycin working standard.

(32) *Candicidin*. The term "candicidin master standard" means a specific lot of candicidin that is designated by the Commissioner as the standard of comparison in determining the potency of the candicidin working standard.

(33) *Cephalothin*. The term "cephalothin master standard" means a specific lot of cephalothin designated by the Commissioner as the standard of comparison in determining the potency of the cephalothin working standard.

(34) *Lincomycin*. The term "lincomycin master standard" means a specific lot of lincomycin designated by the Commissioner as the standard of comparison in determining the potency of the lincomycin working standard.

(35) *Methacycline*. The term "methacycline master standard" means a specific lot of methacycline designated by the Commissioner as the standard of comparison in determining the potency of the methacycline working standard.

(36) *Doxycycline*. The term "doxycycline master standard" means a specific lot of α -6-deoxyoxytetracycline designated by the Commissioner as the standard of comparison in determining the potency of the doxycycline working standard.

(37) *Cephaloridine*. The term "cephaloridine master standard" means a specific lot of cephaloridine that is designated by the Commissioner as

the standard of comparison in determining the potency of the cephaloridine working standard.

(38) *Plicamycin*. The term "plicamycin master standard" means a specific lot of plicamycin designated by the Commissioner as the standard of comparison in determining the potency of the plicamycin working standard.

(39) *Clindamycin*. The term "clindamycin master standard" means a specific lot of clindamycin designated by the Commissioner as the standard of comparison in determining the potency of the clindamycin working standard.

(40) *Cephaloglycin*. The term "cephaloglycin master standard" means a specific lot of cephaloglycin designated by the Commissioner as the standard of comparison in determining the potency of the cephaloglycin working standard.

(41) *Carbenicillin*. The term "carbenicillin master standard" means a specific lot of carbenicillin designated by the Commissioner as the standard of comparison in determining the potency of the carbenicillin working standard.

(42) *Cephalexin*. The term "cephalexin master standard" means a specific lot of cephalexin that is designated by the Commissioner as the standard of comparison in determining the potency of the cephalexin working standard.

(43) [Reserved]

(44) *Capreomycin*. The term "capreomycin master standard" means a specific lot of capreomycin designated by the Commissioner as the standard of comparison in determining the potency of the capreomycin working standard.

(45) *Rifampin*. The term "rifampin master standard" means a specific lot of rifampin designated by the Commissioner as the standard of comparison in determining the potency of the rifampin working standard.

(46) *Minoocycline*. The term "minoocycline master standard" means a specific lot of minocycline designated by the Commissioner as the standard of comparison in determining the potency of the minocycline working standard.

(47) *Spectinomycin*. The term "spectinomycin master standard" means a

specific lot of spectinomycin designated by the Commissioner as the standard of comparison in determining the potency of the spectinomycin working standard.

(48) *Clindamycin palmitate hydrochloride*. The term "clindamycin palmitate hydrochloride master standard" means a specific lot of clindamycin palmitate hydrochloride designated by the Commissioner as the standard of comparison in determining the potency of the clindamycin palmitate hydrochloride working standard.

(49) *Carbentellin indanyl*. The term "carbentellin indanyl master standard" means a specific lot of carbentellin indanyl designated by the Commissioner as the standard of comparison in determining the potency of the carbentellin indanyl working standard.

(50) *Cephapirin*. The term "cephapirin master standard" means a specific lot of cephapirin that is designated by the Commissioner as the standard of comparison in determining the potency of the cephapirin working standard.

(51) *Cefazolin*. The term "cefazolin master standard" means a specific lot of cefazolin that is designated by the Commissioner as the standard of comparison in determining the potency of the cefazolin working standard.

(52) *Mitomycin*. The term "mitomycin master standard" means a specific lot of crystalline mitomycin that is designated by the Commissioner as the standard of comparison in determining the potency of the mitomycin working standard.

(53) *Amoxicillin*. The term "amoxicillin master standard" means a specific lot of amoxicillin that is designated by the Commissioner as the standard of comparison in determining the potency of the amoxicillin working standard.

(54) [Reserved]

(55) *Cephhradine*. The term "cephhradine master standard" means a specific lot of cephradine that is designated by the Commissioner as the standard of comparison in determining the potency of the cephradine working standard.

(56) *Doxorubicin*. The term "doxorubicin master standard" means a specific lot of crystalline doxorubicin that is

designated by the Commissioner as the standard of comparison in determining the potency of the doxorubicin working standard.

(57) *Bleomycin*. The term "bleomycin master standard" means a specific lot of bleomycin designated by the Commissioner as the standard of comparison in determining the potency of the bleomycin working standard.

(58) *Tobramycin*. The term "tobramycin master standard" means a specific lot of tobramycin designated by the Commissioner as the standard of comparison in determining the potency of the tobramycin working standard.

(59) *Ampikacin*. The term "ampikacin master standard" means a specific lot of ampicillin designated by the Commissioner as the standard of comparison in determining the potency of the ampicillin working standard.

(60) *Vidarabine*. The term "vidarabine master standard" means a specific lot of vidarabine that is designated by the Commissioner as the standard of comparison in determining the potency of the vidarabine working standard.

(61) *Ticarcillin*. The term "ticarcillin master standard" means a specific lot of ticarcillin designated by the Commissioner as the standard of comparison in determining the potency of the ticarcillin working standard.

(62) *Cefadroxil*. The term "cefadroxil master standard" means a specific lot of cefadroxil that is designated by the Commissioner as the standard of comparison in determining the potency of the cefadroxil working standard.

(63) *Natamycin*. The term "natamycin master standard" means a specific lot of natamycin designated by the Commissioner in determining the potency of the natamycin working standard.

(64) *Cefoxitin*. The term "cefoxitin master standard" means a specific lot of cefoxitin that is designated by the Commissioner as the standard of comparison in determining the potency of the cefoxitin working standard.

(65) *Cefamandole*. The term "cefamandole master standard" means a specific lot of cefamandole that is designated by the Commissioner as the

standard of comparison in determining the potency of the cefamandole working standard.

(66) *Cefaclor*. The term "cefaclor master standard" means a specific lot of cefaclor that is designated by the Commissioner as the standard of comparison in determining the potency of the cefaclor working standard.

(67) *Cyclacillin*. The term "cyclacillin master standard" means a specific lot of cyclacillin that is designated by the Commissioner as the standard of comparison in determining the potency of the cyclacillin working standard.

(68) *Daunorubicin*. The term "daunorubicin master standard" means a specific lot of daunorubicin that is designated by the Commissioner as the standard of comparison in determining the potency of the daunorubicin working standard.

(69) *Sisomicin*. The term "sisomicin master standard" means a specific lot of sisomicin that is designated by the Commissioner as the standard of comparison in determining the potency of the sisomicin working standard.

(70) *Meclocycline*. The term "meclocycline master standard" means a specific lot of meclocycline that is designated by the Commissioner as the standard of comparison in determining the potency of the meclocycline working standard.

(71) *Cefotaxime*. The term "cefotaxime master standard" means a specific lot of cefotaxime that is designated by the Commissioner as the standard of comparison in determining the potency of the cefotaxime working standard.

(72) *Mezlocillin*. The term "mezlocillin master standard" means a specific lot of mezlocillin that is designated by the Commissioner as the standard of comparison in determining the potency of the mezlocillin working standard.

(73) *Moxalactam*. The term "moxalactam master standard" means a specific lot of moxalactam that is designated by the Commissioner as the standard of comparison in determining the potency of the moxalactam working standard.

(74) *Piperacillin*. The term "piperacillin master standard" means a specific lot of piperacillin that is designated by the Commissioner as the standard

of comparison in determining the potency of the piperacillin working standard.

(75) *Azlocillin*. The term "azlocillin master standard" means a specific lot of azlocillin that is designated by the Commissioner as the standard of comparison in determining the potency of the azlocillin working standard.

(76) *Cefoperazone*. The term "cefoperazone master standard" means a specific lot of cefoperazone that is designated by the Commissioner as the standard of comparison in determining the potency of the cefoperazone working standard.

(77) *Netilmicin*. The term "netilmicin master standard" means a specific lot of netilmicin that is designated by the Commissioner as the standard of comparison in determining the potency of the netilmicin working standard.

(78) *Cefuroxime*. The term "cefuroxime master standard" means a specific lot of cefuroxime that is designated by the Commissioner as the standard of comparison in determining the potency of the cefuroxime working standard.

(79) *Ceftizoxime*. The term "ceftizoxime master standard" means a specific lot of ceftizoxime that is designated by the Commissioner as the standard of comparison in determining the potency of the ceftizoxime working standard.

(80) *Cyclosporine*. The term "cyclosporine master standard" means a specific lot of cyclosporine that is designated by the Commissioner as the standard of comparison in determining the potency of the cyclosporine working standard.

(81) *Ceforanide*. The term "ceforanide master standard" means a specific lot of ceforanide that is designated by the Commissioner as the standard of comparison in determining the potency of the ceforanide working standard.

(82) *Cefonidicid*. The term "cefonicid master standard" means a specific lot of cefonicid that is designated by the Commissioner as the standard of comparison in determining the potency of the cefonicid working standard.

(83) *Clavulanic acid*. The term "clavulanic acid master standard" means a specific lot of clavulanic acid or a salt thereof that is designated by the Com-

missioner as the standard of comparison in determining the potency of the clavulanic acid working standard.

(84) *Amidnoccillin*. The term "amidnoccillin master standard" means a specific lot of amidnoccillin that is designated by the Commissioner as the standard of comparison in determining the potency of the amidnoccillin working standard.

(85) *Ceftriaxone*. The term "ceftriaxone master standard" means a specific lot of ceftriaxone that is designated by the Commissioner as the standard of comparison in determining the potency of the ceftriaxone working standard.

(b) *Working standards*. The potency or purity of each preparation has been determined by comparison with its master standard, and each has been designated by the Commissioner as working standards for use in determining the potency or purity of antibiotic substances subject to the regulations in this chapter. Unless otherwise noted, the working standard and the U.S.P. reference standard for the antibiotic drug named are identical.

(1) *Penicillin*. (1) The term "penicillin G working standard" means a specific lot of a homogeneous preparation of penicillin G.

(ii) [Reserved]

(iii) The term "penicillin V working standard" means a specific lot of a homogeneous preparation of penicillin V.

(iv) [Reserved]

(v) The term "methicillin working standard" means a specific lot of a homogeneous preparation of methicillin.

(vi) The term "oxacillin working standard" means a specific lot of a homogeneous preparation of oxacillin.

(vii) The term "ampicillin working standard" means a specific lot of a homogeneous preparation of ampicillin.

(viii) The term "nafcillin working standard" means a specific lot of a homogeneous preparation of nafcillin.

(ix) The term "cloxacillin working standard" means a specific lot of a homogeneous preparation of cloxacillin.

(x) The term "penicillin G procaine working standard" means a specific lot of a homogeneous preparation of penicillin G procaine.

(xi) The term "dicloxacillin working standard" means a specific lot of a ho-

mogeneous preparation of dicloxacillin.

(xii) The term "bacampicillin hydrochloride working standard" means a specific lot of a homogeneous preparation of bacampicillin hydrochloride.

(2) *Amphotericin A*. The term "amphotericin A working standard" means a specific lot of a homogeneous preparation of amphotericin A.

(3) *Amphotericin B*. The term "amphotericin B working standard" means a specific lot of a homogeneous preparation of amphotericin B.

(4) *Streptomycin*. The term "streptomycin working standard" means a specific lot of a homogeneous preparation of streptomycin.

(5) *Dihydrostreptomycin*. The term "dihydrostreptomycin working standard" means a specific lot of a homogeneous preparation of dihydrostreptomycin.

(6) *Chlortetracycline*. The term "chlortetracycline working standard" means a specific lot of a homogeneous preparation of chlortetracycline.

(7) *Demeclocycline*. The term "demeclocycline working standard" means a specific lot of a homogeneous preparation of demeclocycline.

(8) *Tetracycline*. The term "tetracycline working standard" means a specific lot of a homogeneous preparation of tetracycline.

(9) *Rollitetracycline*. The term "rollitetracycline working standard" means a specific lot of a homogeneous preparation of rollitetracycline.

(10) *Chloramphenicol*. The term "chloramphenicol working standard" means a specific lot of a homogeneous preparation of chloramphenicol.

(11) *Bacitracin*. The term "bacitracin working standard" means a specific lot of a homogeneous preparation of bacitracin.

(12) *Amphotomycin*. The term "amphotomycin working standard" means a specific lot of a homogeneous preparation of amphotomycin.

(13) *Colistin*. The term "colistin working standard" means a specific lot of a homogeneous preparation of colistin.

(14) *Colistimethate*. The term "colistimethate working standard" means a specific lot of a homogeneous preparation of colistimethate.

(15) *Cycloserine*. The term "cycloserine working standard" means a specific lot of a homogeneous preparation of cycloserine.

(16) *Erythromycin*. The term "erythromycin working standard" means a specific lot of a homogeneous preparation of erythromycin.

(17) *Grammidin*. The term "grammidin working standard" means a specific lot of a homogeneous preparation of gramicidin.

(18) *Griseofulvin*. The term "griseofulvin working standard" means a specific lot of a homogeneous preparation of griseofulvin.

(19) *Kanamycin*. The term "kanamycin working standard" means a specific lot of a homogeneous preparation of kanamycin.

(20) *Neomycin*. The term "neomycin working standard" means a specific lot of a homogeneous preparation of neomycin.

(21) *Novobiocin*. The term "novobiocin working standard" means a specific lot of a homogeneous preparation of novobiocin.

(22) *Nystatin*. The term "nystatin working standard" means a specific lot of a homogeneous preparation of nystatin.

(23) *Oleandomycin*. The term "oleandomycin working standard" means a specific lot of a homogeneous preparation of oleandomycin.

(24) *Troleandomycin*. The term "troleandomycin working standard" means a specific lot of a homogeneous preparation of troleandomycin.

(25) *Oxytetracycline*. The term "oxytetracycline working standard" means a specific lot of a homogeneous preparation of oxytetracycline.

(26) *Paromomycin*. The term "paromomycin working standard" means a specific lot of a homogeneous preparation of paromomycin.

(27) *Polymyxin B*. The term "polymyxin B working standard" means a specific lot of a homogeneous preparation of polymyxin B.

(28) *Vancomycin*. The term "vancomycin working standard" means a specific lot of a homogeneous preparation of vancomycin.

(29) [Reserved]

(30) *Gentamicin*. The term "gentamicin working standard" means a spe-

463 as amended, 82 Stat. 350-351 (21 U.S.C. 357, 360(b)(n), 371 (1) and (g))
 139 FR 18925, May 30, 1974, as amended at 39 FR 34031, Sept. 23, 1974; 39 FR 44012, Dec. 20, 1974; 40 FR 26270, June 23, 1975; 40 FR 52009, Nov. 7, 1975; 40 FR 57796; Dec. 12, 1975; 41 FR 14183, Apr. 2, 1976; 41 FR 49482, Nov. 9, 1976; 42 FR 14092, Mar. 15, 1977; 42 FR 44223, Sept. 2, 1977; 42 FR 59854, Nov. 22, 1977; 43 FR 20976, May 16, 1978; 43 FR 41195, Sept. 15, 1978; 43 FR 19782, Nov. 28, 1978; 44 FR 10372, Feb. 22, 1979; 44 FR 20663, Apr. 6, 1979; 45 FR 1979, Jan. 14, 1980; 46 FR 2979, 2987, Jan. 13, 1981; 46 FR 3831, 3835, Jan. 16, 1981; 46 FR 15880, Mar. 10, 1981; 46 FR 25602, 25605, May 8, 1981; 46 FR 58298, Dec. 1, 1981; 46 FR 61069, 61071, Dec. 15, 1981; 47 FR 15768, Apr. 13, 1982; 47 FR 53347, Nov. 26, 1982; 48 FR 789, Jan. 7, 1983; 48 FR 18800, Apr. 26, 1983; 48 FR 38459, Aug. 24, 1983; 48 FR 46270, Oct. 12, 1983; 48 FR 51290, Nov. 8, 1983; 49 FR 5096, Feb. 10, 1984; 49 FR 6091, Feb. 17, 1984; 49 FR 22631, May 31, 1984; 49 FR 25846, June 25, 1984; 49 FR 34347, 34350, Aug. 30, 1984; 49 FR 39670, Oct. 10, 1984; 50 FR 1504, Jan. 11, 1985; 50 FR 7764, Feb. 26, 1985; 50 FR 9998, Mar. 13, 1985)

§ 130.6 Definitions of the terms "unit" and "microgram" as applied to antibiotic substances.

Unless it has been otherwise specified in the individual definitions in this section, the activity assigned to each "unit" or "microgram" is equivalent to an International Unit, if such has been defined by the World Health Organization.

(a) "Unit" (1) *Penicillin*—(i) *Penicillin G*. The term "unit" applies to penicillin G means the penicillin activity (potency) contained in 0.600 microgram of the penicillin G master standard.
 (ii) [Reserved]

(iii) *Penicillin V*. The term "unit" applied to penicillin V means the penicillin activity (potency) contained in 0.590 microgram of the penicillin V master standard.

(2) *Bacitracin*. The term "unit" applied to bacitracin means a bacitracin activity (potency) contained in 13.51 micrograms of the bacitracin master standard, except that when the activity (potency) of bacitracin is expressed in terms of its weight, as in the feed and drinking water of animals, 1 gram of activity is equivalent to 42,000 units.

(3) *Nystatin*. The term "unit" applied to nystatin means the nystatin activity (potency) contained in 0.2817 microgram of the nystatin master standard when dried for 2 hours at 40° C. and a pressure of 5 millimeters or less.

(4) *Polymyxin B*. The term "unit" applied to polymyxin B means the polymyxin activity (potency) contained in 0.1274 microgram of the polymyxin B master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(5) *Bleomycin*. The term "unit" applied to bleomycin means the bleomycin activity (potency) contained in 0.637 milligram of the bleomycin master standard.

(b) "*Microgram*"—(1) *Streptomycin*. The term "microgram" applied to streptomycin means the streptomycin activity (potency) contained in 1.250 micrograms of the streptomycin master standard after it is dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(2) *Dihydrostreptomycin*. The term "microgram" applied to dihydrostreptomycin means the dihydrostreptomycin activity (potency) contained in 1.25 micrograms of the dihydrostreptomycin master standard after it is dried for 4 hours at 100° C. and a pressure of 50 microns or less.

(3) *Chlortetracycline*. The term "microgram" applied to chlortetracycline means the chlortetracycline activity (potency) contained in 1.0 microgram of the chlortetracycline master standard.

(4) *Demeclocycline*. The term "microgram" applied to demeclocycline means the demeclocycline activity (potency) contained in 1.0 microgram of the demeclocycline master standard after it is dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(5) *Tetracycline*. The term "microgram" applied to tetracycline means the tetracycline activity (potency) contained in 1.0 microgram of tetracycline master standard.

(6) *Rolitetraacycline*. The term "microgram" applied to rolitetraacycline means the rolitetraacycline activity (potency) contained in 1.0 microgram of the rolitetraacycline master standard.

when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(7) *Chloramphenicol*. The term "microgram" applied to chloramphenicol means the chloramphenicol activity (potency) contained in 1.0 microgram of the chloramphenicol master standard.

(8) *Methicillin*. The term "microgram" applied to methicillin means the methicillin activity (potency) contained in 1.105 micrograms of the methicillin master standard.

(9) *Oxacillin*. The term "microgram" applied to oxacillin means the oxacillin activity (potency) contained in 1.111 micrograms of the oxacillin master standard.

(10) *Amphoterycin*. The term "microgram" applied to amphoterycin means the amphoterycin activity (potency) contained in 0.9355 microgram of the amphoterycin master standard when dried for 4 hours at 60° C. and a pressure of 5 millimeters or less.

(11) *Amphoterycin A*. The term "microgram" applied to amphoterycin A means the amphoterycin A activity (potency) contained in 1.0 microgram of the amphoterycin A master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(12) *Amphoterycin B*. The term "microgram" applied to amphoterycin B means the amphoterycin B activity (potency) contained in 1.014 micrograms of the amphoterycin B master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(13) *Colistin*. The term "microgram" applied to colistin means the colistin base activity (potency) contained in 1.495 micrograms of the colistin master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less. The numerical value of a microgram of colistin is not equivalent to the International Unit.

(14) *Colistimethate*. The term "microgram" applied to colistimethate means the activity (potency) calculated as colistin base that is contained in 1.938 micrograms of the colistimethate master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less. The numerical value of a microgram of colistimethate is not equivalent to the International Unit.

(15) *Cycloserine*. The term "microgram" applied to cycloserine means the cycloserine activity (potency) contained in 1.0 microgram of the cycloserine master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(16) *Erythromycin*. The term "microgram" applied to erythromycin means the erythromycin base activity (potency) contained in 1.02 micrograms of the erythromycin master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(17) *Gramicidin*. The term "microgram" applied to gramicidin means the gramicidin activity (potency) contained in 1.0 microgram of the gramicidin master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(18) *Griseofulvin*. The term "microgram" applied to griseofulvin means the griseofulvin activity (potency) contained in 1.0 microgram of the griseofulvin master standard.

(19) *Kanamycin*. The term "microgram" applied to kanamycin means the kanamycin base activity (potency) contained in 1.299 micrograms of the kanamycin master standard.

(20) *Neomycin*. The term "microgram" applied to neomycin means the neomycin base activity (potency) contained in 1.429 micrograms of the neomycin master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(21) *Novobiocin*. The term "microgram" applied to novobiocin means the novobiocin acid activity (potency) contained in 1.033 micrograms of the novobiocin master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(22) *Oleandomycin*. The term "microgram" applied to oleandomycin means the oleandomycin base activity (potency) contained in 1.176 micrograms of the oleandomycin master standard.

(23) *Troleandomycin*. The term "microgram" applied to troleandomycin means the activity (potency), calculated as the molecular equivalent of the oleandomycin base, contained in 1.2315 micrograms of the troleandomycin master standard.

(24) *Oxytetracycline*. The "micro-gram" applied to oxytetracycline base active means the oxytetracycline base active (potency) contained in 1.13 micrograms of the oxytetracycline master standard.

(25) *Paromomycin*. The term "microgram" applied to paromomycin program" applied to paromomycin means the paromomycin activity (potency) contained in 1.333 micrograms of the paromomycin master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(26) *Tyrolthricin*. The term "microgram" applied to tyrolthricin means the activity (potency) contained in 0.2 microgram of the granlicidin master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(27) *Vancomycin*. The term "microgram" applied to vancomycin means the vancomycin base activity (potency) contained in 1.25 micrograms of the vancomycin master standard.

(28) [Reserved]

(29) *Ampicillin*. The term "microgram" applied to ampicillin means the ampicillin activity (potency) contained in 1.1764 micrograms of the ampicillin master standard.

(30) *Nafcillin*. The term "microgram" applied to nafcillin means the nafcillin activity (potency) contained in 1.0989 micrograms of the nafcillin master standard.

(31) *Gentamicin*. The term "microgram" applied to gentamicin means the gentamicin activity (potency) contained in 1.56 micrograms of the gentamicin master standard when dried for 3 hours at 110° C. and a pressure of 5 millimeters or less.

(32) *Dactinomycin*. The term "microgram" applied to dactinomycin means the dactinomycin activity (potency) contained in 1.000 microgram of the dactinomycin master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(33) *Candidicin*. The term "microgram" applied to candidicin means the candidicin activity (potency) contained in 1.0 microgram of the candidicin master standard when dried for 3 hours at 40° C. and a pressure of 5 millimeters or less.

(34) *Cephalothin*. The term "microgram" applied to cephalothin means

the cephalothin activity (potency) contained in 1.066 micrograms of the cephalothin master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(35) *Lincomycin*. The term "microgram" applied to lincomycin means the lincomycin base activity (potency) contained in 1.156 micrograms of the lincomycin master standard.

(36) *Cloxacillin*. The term "microgram" applied to cloxacillin means the cloxacillin activity (potency) contained in 1.135 micrograms of the cloxacillin master standard.

(37) *Methacycline*. The term "microgram" applied to methacycline means the methacycline activity (potency) contained in 1.082 micrograms of the methacycline master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(38) *Doxycycline*. The term "microgram" applied to doxycycline means the doxycycline activity (potency) contained in 1.155 micrograms of the doxycycline master standard.

(39) *Cephaloridine*. The term "microgram" applied to cephaloridine means the cephaloridine activity (potency) contained in 1.0086 micrograms of the cephaloridine master standard when dried for 3 hours at 60° C. and a pressure of 5 millimeters or less.

(40) *Dicloxacillin*. The term "microgram" applied to dicloxacillin means the dicloxacillin activity (potency) contained in 1.087 micrograms of the dicloxacillin master standard.

(41) *Plicamycin*. The term "microgram" applied to plicamycin means the plicamycin activity (potency) contained in 1.000 microgram of the plicamycin master standard when dried for 4 hours at 25° C. and a pressure of 5 millimeters or less.

(42) *Cindamycin*. The term "microgram" applied to cindamycin means the cindamycin activity (potency) contained in 1.139 micrograms of the cindamycin master standard.

(43) *Cephaloglycin*. The term "microgram" applied to cephaloglycin means the cephaloglycin activity (potency) contained in 1.02564 micrograms of the cephaloglycin master standard.

(44) *Carbenicillin*. The term "microgram" applied to carbenicillin means the carbenicillin activity (potency) contained in 1.135 micrograms of the carbenicillin master standard.

(45) *Cephalexin*. The term "microgram" applied to cephalexin means the cephalexin activity (potency) contained in 1.0707 micrograms of the cephalexin master standard.

(46) [Reserved]

(47) *Capreomycin*. The term "microgram" applied to capreomycin means the capreomycin activity (potency) contained in 1.0870 micrograms of the capreomycin master standard when dried for 4 hours at 100° C. and a pressure of 5 millimeters or less.

(48) *Rifampin*. The term "microgram" applied to rifampin means the rifampin activity (potency) contained in 1.0101 micrograms of the rifampin master standard.

(49) *Minoocycline*. The term "microgram" applied to minocycline means the minocycline activity (potency) contained in 1.1588 micrograms of the minocycline master standard.

(50) *Spectinomycin*. The term "microgram" applied to spectinomycin means the spectinomycin activity (potency) contained in 1.490 micrograms of the spectinomycin master standard.

(51) *Cindamycin palmitate hydrochloride*. The term "microgram" applied to cindamycin palmitate hydrochloride means the cindamycin activity (potency) contained in 1.661 micrograms of the cindamycin palmitate hydrochloride master standard.

(52) *Carbenticillin indanyl*. The term "microgram" applied to carbenticillin indanyl means the carbenticillin activity (potency) contained in 1.4514 micrograms of the carbenticillin indanyl master standard.

(53) *Cephapirin*. The term "microgram" applied to cephapirin means the cephapirin activity (potency) contained in 1.0616 micrograms of the cephapirin master standard.

(54) *Cefazolin*. The term "microgram" applied to cefazolin means the cefazolin activity (potency) contained in 1.005 micrograms of the cefazolin master standard.

(55) *Mitomycin*. The term "microgram" applied to mitomycin means the mitomycin activity (potency) con-

tained in 1.0416 micrograms of the mitomycin master standard.

(56) *Amoxicillin*. The term "microgram" applied to amoxicillin means the amoxicillin activity (potency) contained in 1.17647 micrograms of the amoxicillin master standard.

(57) [Reserved]

(58) *Cephradine*. The term "microgram" applied to cephradine means the cephradine activity (potency) contained in 1.1111 micrograms of the cephradine master standard.

(59) *Doxorubicin*. The term "microgram" applied to doxorubicin means the activity (potency) calculated as doxorubicin hydrochloride contained in 1.0204 micrograms of the doxorubicin master standard.

(60) *Tobramycin*. The term "microgram" applied to tobramycin means the tobramycin activity (potency) contained in 1.126 micrograms of the tobramycin master standard.

(61) *Amikacin*. The term "microgram" applied to amikacin means the amikacin activity (potency) contained in 1.091 micrograms of the amikacin master standard.

(62) *Vidarabine*. The term "microgram" applied to vidarabine means the vidarabine activity (potency) contained in 1.0674 micrograms of the vidarabine master standard.

(63) *Ticarcillin*. The term "microgram" applied to ticarcillin means the ticarcillin activity (potency) contained in 1.136 micrograms of the ticarcillin master standard.

(64) *Cefadroxil*. The term "microgram" applied to cefadroxil means the cefadroxil activity (potency) contained in 1.0537 micrograms of the cefadroxil master standard.

(65) *Natamycin*. The term "microgram" applied to natamycin means the natamycin activity (potency) contained in 1.0846 micrograms of the natamycin master standard.

(66) *Cefoxitin*. The term "microgram" applied to cefoxitin means the cefoxitin activity (potency) contained in 1.072 micrograms of the cefoxitin master standard.

(67) *Cefamandole*. The term "microgram" applied to cefamandole means the cefamandole activity (potency) contained in 1.1364 micrograms of cefamandole master standard.

respect to antibiotic drugs for...
 subject to the new drug provisions of
 the act through its Drug Efficacy
 Study Implementation (DESI) pro-
 gram under which the agency is evalu-
 ating those antibiotic drugs for effec-
 tiveness. Until FDA completes that evalua-
 tion it will permit continued market-
 ing of those antibiotic drugs under
 paragraph (c) of this section. The
 agency is also implementing the 1962
 amendments with respect to antibiotic
 drugs formerly not subject to either
 the certification or new drug provi-
 sions of the act and the agency is eval-
 uating those antibiotic drugs for both
 safety and efficacy. Until FDA com-
 pletes that evaluation, it will permit
 continued marketing of those antibiot-

**Subpart B—Antibiotic Drugs Affected
 by the Drug Amendments of 1962**

1985] Oct. 10, 1984; 50 FR 1504, Jan. 11, 1985; 50
 FR 7764, Feb. 26, 1985; 50 FR 9989, Mar. 13,
 1985; 48 FR 24062, May 31, 1983; 48 FR 38460,
 Aug. 24, 1983; 48 FR 46270, Oct. 12, 1983; 49
 FR 5096, Feb. 10, 1984; 49 FR 22631, May
 1984; 49 FR 25846, June 25, 1984; 49 FR
 34347, 34350, Aug. 30, 1984; 49 FR 39670,
 Oct. 10, 1984; 50 FR 1504, Jan. 11, 1985; 50
 FR 7764, Feb. 26, 1985; 50 FR 9989, Mar. 13,
 1985]

430.10 Certification or release of antibi-
 otic drugs affected by the drug amend-
 ments of 1962.

(a) Before the 1962 amendments to
 the Federal Food, Drug, and Cos-
 metic Act only permitted the Food
 and Drug Administration to provide
 for the certification of batches of anti-
 biotic drugs containing penicillin, chlor-
 streptomycin, chlorotetracycline, or any de-
 rivative of them. FDA certified those
 drugs under regulations promulgated
 on the basis of scientific proof of the
 drugs' safety and effectiveness. Most
 of these drugs established under sec-
 tion 507(h) of the act was not condi-
 tioned upon an affirmative finding of
 the effectiveness of the drug. FDA is
 proceeding under its DESI program to
 amend or repeal those regulations to
 provide for certification of those drugs
 only if they had been shown to be
 both safe and effective.

(c) Unless exempted from certifica-
 tion, FDA will certify or release antibi-
 otic drugs which on April 30, 1963
 were the subject of an approved new
 drug application under section 505 of
 the act, under regulations providing
 for certification of the drugs. Al-
 though the initial regulation for each
 of these drugs established under sec-
 tion 507(h) of the act was not condi-
 tioned upon an affirmative finding of
 the effectiveness of the drug, FDA is
 proceeding under its DESI program to
 amend or repeal those regulations to
 provide for certification of those drugs
 only if they had been shown to be
 both safe and effective.

(d) Unless exempted from certifica-
 tion, FDA will release without certifi-
 cation an antibiotic drug that was
 marketed on April 30, 1963, but not
 subject to certification, and not sub-
 ject to an approved new drug applica-
 tion on that date, unless FDA has
 made a determination that the drug
 has not been shown to be safe or lacks
 substantial evidence of effectiveness
 under the DESI program. FDA is pro-
 ceeding under its DESI program to es-
 tablish regulations under section 507
 to provide for certification of those
 drugs only if they have been shown to
 be safe and effective.

(b) The 1962 amendments amended
 section 507 of the act to require the
 certification, release without certifica-
 tion, or exemption from certification,
 of all antibiotic drugs on the basis of
 scientific proof of safety and effective-
 ness. The amendments provided that
 FDA implement them for antibiotic
 drugs that were marketed on April 30,
 1963 and were not subject to the certi-
 fication provisions on that date. FDA
 is implementing the amendments with

(Secs. 409, 501, 502, 503, 506, 507, 512-
 516, 520, 701, 706, 52 Stat. 1049-1053 as
 amended, 1055, 1056 as amended, 55 Stat.
 851, 59 Stat. 463 as amended, 72 Stat. 1785-
 1788 as amended, 74 Stat. 399-407 as amend-
 ed)

applied to cefaclor means the cefaclor
 master standard expressed on an an-
 hydrous basis.

(80) *Cefuroxime*. The term "micro-
 gram" applied to cefuroxime means
 the cefuroxime activity (potency) con-
 tained in 1.0893 micrograms of the ce-
 furoxime master standard.

(81) *Ceftizoxime*. The term "micro-
 gram" applied to ceftizoxime means
 the ceftizoxime activity (potency) con-
 tained in 1.011 micrograms of the cefti-
 zoxime master standard.

(82) *Cyclosporine*. The term "micro-
 gram" applied to cyclosporine means
 the cyclosporine activity (potency)
 contained in 1.0173 micrograms of cy-
 closporine master standard.

(83) *Ceforanide*. The term "micro-
 gram" applied to ceforanide means the
 ceforanide activity (potency) con-
 tained in 1.005 micrograms of the ce-
 foranide master standard.

(84) *Cefonicid*. The term "micro-
 gram" applied to cefonicid means the
 cefonicid activity (potency) contained
 in 1.150 micrograms of the cefonicid
 master standard.

(85) *Clavulanic acid*. The term "mi-
 crogram" applied to clavulanic acid
 means the clavulanic acid activity (po-
 tency) contained in 1.053 micrograms
 of clavulanic acid master standard.

(86) *Amdinocillin*. The term "micro-
 gram" applied to amdinocillin means
 the amdinocillin activity (potency)
 contained in 1.004 micrograms of the
 amdinocillin master standard.

(87) *Ceftriaxone*. The term "micro-
 gram" applied to ceftriaxone means
 the ceftriaxone activity (potency) con-
 tained in 1.19 micrograms of the cefti-
 raxone master standard.

(88) *Piperacillin*. The term "micro-
 gram" applied to piperacillin means
 the piperacillin activity (potency) con-
 tained in 1.0460 micrograms of the pi-
 peracillin master standard.

(89) *Cefoperazone*. The term "micro-
 gram" applied to cefoperazone means
 the cefoperazone activity (potency)
 contained in 1.056 micrograms of the
 cefoperazone master standard.

(90) *Azlocillin*. The term "micro-
 gram" applied to azlocillin means the
 azlocillin activity (potency) contained
 in 1.128 micrograms of the azlocillin
 master standard.

(91) *Netilmicin*. The term "micro-
 gram" applied to netilmicin means the
 netilmicin activity (potency) contained

in 1.01 micrograms of the cycloacillin
 master standard.

(92) *Dannorubicin*. The term "mi-
 crogram" applied to dannorubicin
 means the dannorubicin activity (po-
 tency) contained in 1.0965 micrograms
 of the dannorubicin master standard.

(93) *Sisomicin*. The term "micro-
 gram" applied to sisomicin means the
 sisomicin activity (potency) contained
 in 1.00 microgram of the sisomicin
 master standard expressed on an an-
 hydrous basis.

(94) *Mecloxycline*. The term "micro-
 gram" applied to mecloxycline means
 the mecloxycline activity (potency)
 contained in 1.0493 micrograms of the
 mecloxycline master standard.

(95) *Cefotaxime*. The term "micro-
 gram" applied to cefotaxime means
 the cefotaxime activity (potency) con-
 tained in 1.089 micrograms of cefotax-
 ime master standard.

(96) *Mezlocillin*. The term "micro-
 gram" applied to mezlocillin means
 the mezlocillin activity (potency) con-
 tained in 1.1086 micrograms of the
 mezlocillin master standard.

(97) *Moxalactam*. The term "micro-
 gram" applied to moxalactam means
 the moxalactam activity (potency)
 contained in 1.1173 micrograms of the
 moxalactam master standard.

(98) *Piperacillin*. The term "micro-
 gram" applied to piperacillin means
 the piperacillin activity (potency) con-
 tained in 1.19 micrograms of the cefti-
 raxone master standard.

(99) *Cefuroxime*. The term "micro-
 gram" applied to cefuroxime means
 the cefuroxime activity (potency) con-
 tained in 1.0893 micrograms of the ce-
 furoxime master standard.

(100) *Ceftizoxime*. The term "micro-
 gram" applied to ceftizoxime means
 the ceftizoxime activity (potency) con-
 tained in 1.011 micrograms of the cefti-
 zoxime master standard.

lution, dilute to volume with pH 7.0 buffer solution and mix. Using this sample solution, proceed as directed in paragraph (f) of this section.

(ii) *Milligrams of cefprozime per container.* Reconstitute the sample as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency is a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Further dilute an aliquot of the solution thus obtained with sufficient pH 7.0 buffer solution to obtain a concentration of 1.0 milligram per milliliter. Transfer 2.0 milliliters of this solution to a 100-milliliter volumetric flask, add 5.0 milliliters of internal standard solution, dilute to volume with pH 7.0 buffer solution and mix. Using this sample solution, proceed as directed in paragraph (f) of this section.

(f) *Procedure.* Using the equipment, reagents, and operating conditions as listed in paragraphs (a), (b), and (c) of this section, inject 10 microliters of the working standard solution into the chromatograph. Allow an elution time sufficient to obtain satisfactory separation of the expected components. The elution order is void volume, cefprozime, and internal standard. After separation of the working standard so- lution has been completed, inject 10 microliters of the sample solution prepared as described in paragraph (e)(1) of this section into the chromatograph and repeat the procedure described for the working standard solution. If the sample is packaged for dispensing, repeat the procedure for each sample solution prepared as described in paragraphs (e)(2) (i) and (ii) of this section. (g) *Calculations*—(1) Calculate the micrograms of cefprozime per milligram of sample as follows:

$$\frac{\text{Micrograms of cefprozime per milligram}}{R_s \times P_s \times 100} = \frac{R_s \times C_s \times (100 - m)}{R_s \times P_s \times 100}$$

Where:

R_s = Area of the cefprozime peak in the chromatogram of the sample (at a retention time equal to that observed for the standard)/Area of internal standard peak;
 R_s = Area of the cefprozime peak in the chromatogram of the cefprozime working standard/Area of internal standard peak;
 P_s = Cefprozime activity in the cefprozime working standard solution in micrograms per milliliter;
 C_s = Milligrams of sample per milliliter of sample solution; and
 m = Percent moisture content of the sample.

(2) Calculate the cefprozime content of the vial as follows:

$$\frac{\text{Milligrams of cefprozime per vial}}{R_s \times P_s \times d} = \frac{R_s \times P_s \times d}{R_s \times 1,000}$$

where:

R_s = Area of the cefprozime peak in the chromatogram of the sample (at a retention time equal to that observed for the standard)/Area of internal standard peak;
 R_s = Area of the cefprozime peak in the chromatogram of the cefprozime working standard/Area of internal standard peak;
 P_s = Cefprozime activity in the cefprozime working standard solution in micrograms per milliliter; and
 d = Dilution factor of the sample.

(Secs. 507, 701 (f) and (g), 52 Stat. 1055-1056 as amended, 59 Stat. 463 as amended (21 U.S.C. 357, 371 (f) and (g))).
 [48 FR 46270, Oct. 12, 1983; 48 FR 49656, Oct. 27, 1983]

§ 436.346 High-pressure liquid chromatographic assay for cyclosporine.

(a) *Equipment.* A suitable high-pressure liquid chromatograph equipped with:

- (1) A suitable pump capable of reproducibly delivering a liquid to a pressure of 4,500 pounds per square inch and a flow rate of at least 5 milliliters per minute;
- (2) A suitable ultraviolet detection system operating at a wavelength of 210 nanometers;
- (3) A suitable recorder;
- (4) A suitable integrator;

(5) An oven or water bath capable of maintaining the column at an operating temperature of 70° C;

(6) A steel capillary tube, 1 meter in length, having an inside diameter of 0.25 millimeter. This tube is inserted between the injection system and the chromatographic column and is equilibrated to 70° C; and

(7) A sample injection valve on which the loop determines the sample size.

(b) *Columns.* The chromatographic column is packed with microparticulate (3 to 10 micrometers in diameter) reversed phase packing materials that exhibit some degree of polarity such as the hydrocarbon bonded silicas with dimethyl, trimethyl, or octyl groups. Connect a saturation column gravity packed with similarly bonded silica particles 40 to 60 microns in diameter to the inlet of the analytical column.

(c) *Mobile phase.* Mix acetonitrile, water, methanol, and o-phosphoric acid (900:525:75:0.075 by volume). Degass by passing through a 0.5-micrometer filter with vacuum and ultrasonicate for no less than 2 minutes before use. The mobile phase may be sparged perceptibly with helium through a 2-micrometer metal filter for the duration of the analysis. Adjust the ratio of acetonitrile to aqueous buffer as necessary to obtain satisfactory retention of the peaks.

(d) *Operating conditions.* Perform the assay at a constant operating temperature of 70° C with a typical flow rate of 2.0 milliliters per minute. Use a detector sensitivity setting that gives a peak height for the working standard that is at least 50 percent of scale with a typical chart speed of 2.5 millimeters per minute. Obtain chromatograms for performance parameters at a chart speed of not less than 25 millimeters per minute to allow a more accurate measurement of peak geometry.

(e) *Preparation of working standard and sample solutions.* Prepare the working standard and sample solutions as directed in the individual monographs for cyclosporine.

(f) *Systems suitability.* Equilibrate and condition the column by passage of about 10 to 15 void volumes of mobile phase followed by about 5 in-

jections of not less than 10 microliters each of working standard solution. Proceed with the analysis when the following minimum performance requirements have been met or exceeded.

(1) *Capacity ratio factor.* Calculate the capacity ratio (k) of the cyclosporine peak as follows:

$$k = \frac{t - t_m}{t_m}$$

where:

t = Retention time of solute; and
 t_m = Retention time of solvent or unretained substance.

The capacity ratio is satisfactory if it is not less than 3 or not more than 10.
 (2) *Coefficient of variation.* The coefficient of variation of at least five replicate injections is less than 1 percent.

(3) *Efficiency.* Calculate the efficiency (n) as follows:

$$n = 5.545 \left(\frac{t}{W_{0.5}} \right)^2$$

where:

t = Retention time of solute; and
 $W_{0.5}$ = Peak width at half height. Both t and $W_{0.5}$ must be measured in the same units.

The efficiency is satisfactory if it is greater than 1,500 theoretical plates when assaying cyclosporine and greater than 700 theoretical plates when assaying finished dosage forms.

(4) *Asymmetry factor.* Calculate the asymmetry factor (A_s) as follows:

$$A_s = \frac{W_{0.1}}{2f}$$

where:

$W_{0.1}$ = Horizontal distance measured from a point on the cyclosporine peak ascent 10 percent above the baseline to an intercept with the cyclosporine peak descent; and

f = Horizontal distance from point of 10 percent ascent above the baseline of the cyclosporine peak to point of maximum peak height.

The asymmetry factor is satisfactory if it is not more than 1.5.

(5) *Resolution.* Calculate the resolution (R_s) as follows:

$$R_s = \frac{2(t_f - t_r)}{(W_f + W_r)}$$

where:
t—Retention time of solute; and the subscripts *i* and *j* designate two different peaks and where *t_i* is larger than *t_j*; and *W*—Width of peak at baseline as determined by extrapolating the relative straight sides to the baseline. Both *t* and *W* must be measured in the same units.

Resolution between the cyclosporine peak and any other peak must be at least 1.1.

(g) *Procedure.* Using the equipment, columns, mobile phase, operating conditions and the working standard and sample solutions listed in paragraphs (a), (b), (c), (d), and (e) of this section, inject 20 microliters of the working standard solution into the chromatograph. Allow an elution time sufficient to obtain satisfactory separation of expected components. After separation of the working standard solution has been completed, inject 20 microliters of the sample solution into the chromatograph and repeat the procedure described for the working standard solution.

(h) *Calculations.* Calculate the cyclosporine content of cyclosporine and its dosage forms as directed in the individual monographs.

(Secs. 507, 701 (f) and (g), 52 Stat. 1055-1056 as amended, 59 Stat. 463 as amended (21 U.S.C. 357, 371 (f) and (g)))
 [49 FR 22631, May 31, 1984; 49 FR 27489, July 5, 1984]

§ 436.347 High-pressure liquid chromatographic assay for cefoxitin.

(a) *Equipment.* A suitable high-pressure liquid chromatograph equipped with:

- (1) A low dead volume cell 8 to 20 microliters;
- (2) A light path length of 1 centimeter;
- (3) A suitable ultraviolet detection system operating at a wavelength of 254 nanometers;
- (4) A suitable recorder of at least 25.4 centimeter deflection;
- (5) A suitable integrator; and
- (6) A 30-centimeter column having an inside diameter of 4.0 millimeters and packed with octadecyl silane

chemically bonded to porous silica or ceramic microparticles, 5 micrometers to 10 micrometers in diameter, U.S.P. XX.

(b) *Reagents*—(1) *One percent potassium phosphate buffer pH 6.0.* Prepare as described in § 436.101(a)(1).

(2) *Mobile phase.* Mix distilled water:glacial acetic acid:acetonitrile (800:10:190). Filter the mobile phase through a suitable glass fiber filter or equivalent that is capable of removing particulate contamination to 1 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph pumping system.

(c) *Operating conditions.* Perform the assay at ambient temperature with a typical flow rate of 1.0 milliliter per minute. Use a detector sensitivity setting that gives a peak height for the working standard that is at least 50 percent of scale. The minimum between peaks must be no more than 2 millimeters above the baseline.

(d) *Preparation of working standard and sample solutions.* Use the working standard and sample solutions prepared as described in the individual monographs for the drug being tested.

(e) *Procedure.* Using the equipment, reagents, and operating conditions as described in paragraphs (a), (b), and (c) of this section, inject 10 microliters of the working standard solution into the chromatograph. Allow an elution time sufficient to obtain separation of the expected components. After separation of the working standard solution has been completed, inject 10 microliters of the sample solution into the chromatograph and repeat the procedure described for the working standard solution.

(f) *Calculations.* Calculate the cefoxitin content as described in the individual monographs for the drug being tested.

(Secs. 507, 701(f) and (g), 52 Stat. 1055-1056 as amended, 59 Stat. 463 as amended (21 U.S.C. 357, 371(f) and (g)))
 [49 FR 47827, Dec. 7, 1984]

§ 436.348 High-pressure liquid chromatographic assay for ceforanide.

(a) *Equipment.* A suitable high-pressure liquid chromatograph equipped with:

(1) A low dead volume cell 8 to 20 microliters;

(2) A light path length of 1 centimeter;

(3) A suitable ultraviolet detection system operating at a wavelength of 254 nanometers;

(4) A suitable recorder of at least 25.4-centimeter deflection;

(5) A suitable integrator; and

(6) A 30-centimeter column having an inside diameter of 4.0 millimeters and packed with octadecyl silane chemically bonded to porous silica or ceramic microparticles, 5 micrometers to 10 micrometers in diameter, U.S.P. XX. A particular column used for analysis of ceforanide should not be used for the analysis of other drugs.

(b) *Mobile phase.* Mix 18.0 milliliters of 10 percent aqueous tetrabutylammonium hydroxide and 8.56 milliliters of 11*N* potassium hydroxide. Add the mixture to approximately 700 milliliters of distilled water. Add 200 milliliters of reagent grade methanol. Adjust the pH of the mixture to pH 7.0 with concentrated phosphoric acid and dilute to 1,000 milliliters with distilled water. Prepare fresh daily. Filter the mobile phase through a suitable glass fiber filter or equivalent which is capable of removing particulate contamination to 1 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph pumping system.

(c) *Operating conditions.* Perform the assay at ambient temperature with a typical flow rate of 1 milliliter per minute. Use a detector sensitivity setting that gives a peak height for the working standard that is at least 50 percent of scale.

(d) *Preparation of working standard and sample solutions*—(1) *Preparation of working standard solution.* Prepare a solution containing 1,000 micrograms of ceforanide activity per milliliter in mobile phase. Inject working standard solution within 5 minutes after dissolution.

(2) *Preparation of sample solution.* Prepare the sample solution as directed in the individual monograph for the drug being tested. Inject sample solution within 5 minutes after dissolution.

(e) *Procedure.* Use the equipment, mobile phase, operating conditions, and working standard and sample solutions described in paragraphs (a), (b), (c), and (d) of this section, and proceed as directed in paragraph (e)(1) of this section.

(1) *System suitability test.* Equilibrate and condition the column by passage of about 10 to 15 void volumes of mobile phase followed by three replicate injections of 10 microliters each of the working standard solution. Allow an elution time sufficient to obtain satisfactory separation of expected components after each injection. Record the peak responses and calculate the tailing factor, efficiency of the column, coefficient of variation, and capacity factor as described for system suitability tests in the U.S.P. XX General Chapter 621 chromatography. Proceed as directed in paragraph (e)(2) of this section if the following minimum performance requirements have been met:

(i) *Tailing factor.* The tailing factor is satisfactory if it is not more than 1.2.

(ii) *Efficiency of the column.* The efficiency of the column is satisfactory if it is greater than 1,900 theoretical plates;

(iii) *Coefficient of variation.* The coefficient of variation of at least three replicate injections is satisfactory if it is not more than 1.5 percent; and

(iv) *Capacity factor.* The capacity factor is satisfactory if it is not less than 1.8 and not more than 5.

If the minimum performance requirements are not met, adjustments must be made to the system to obtain satisfactory operation before proceeding as described in paragraph (e)(2) of this section.

(2) *Determination of the chromatogram.* Inject 10 microliters of the working standard solution into the chromatograph. Allow an elution time sufficient to obtain satisfactory separation of the expected components after separation of the working standard solution has been completed. Inject 10 microliters of the sample solution into the chromatograph and repeat the procedure described for the working standard solution.

360(b)(n), 371(f) and (g))
 139 FR 19115, May 30, 1974, as amended at
 46 FR 60568, Dec. 11, 1981

§ 448.20a Sterile colistimethate sodium.

(a) *Requirements for certification—*
quality, and purity. Colistimethate sodium is the sodium salt of a kind of colistin methane sulfonate or a mixture of two or more such salts. It is a white to slightly yellow, odorless, fine powder which is freely soluble in water. It is so purified and dried that:

- (i) Its potency is not less than 390 micrograms of colistin base equivalent per milligram. If it is packaged for dispensing, its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of colistin base equivalent that it is represented to contain.
- (ii) It is sterile.
- (iii) It passes the safety test.
- (iv) It is nonpyrogenic.
- (v) Its loss on drying is not more than 7.0 percent.
- (vi) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 6.5 and not more than 8.5.
- (vii) It gives a positive identity test for colistimethate sodium.
- (viii) It passes the test for free colistin.

- (ix) Its heavy metals content is not more than 30 parts per million.
- (2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.
- (3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

- (i) Results of tests and assays on the batch for potency, sterility, safety, pyrogens, loss on drying, pH, identity, free colistin, and heavy metals.
- (ii) Samples required:
- (a) If the batch is packaged for repackaging or for use in the manufacture of another drug:
- (1) For all tests except sterility: 10 containers, each containing approximately 500 milligrams.
- (2) For sterility testing: 20 packages, each containing approximately 300 milligrams.

(b) If the batch is packaged for dispensing:

- (1) For all tests except sterility: minimum of 12 vials or if each contains less than 150 milligrams colistimethate, a minimum of 60 vials.
- (2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling action.

(b) *Tests and methods of assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: If the batch is packaged for repackaging use in manufacturing another product, dissolve an accurately weighed sample in 2 milliliters of sterile distilled water and further dilute with sufficient percent potassium phosphate buffer, pH 6.0 (solution 6), to give a solution of convenient concentration. It is packaged for dispensing, repackaging as directed in the labeling. If using a suitable hypodermic syringe and syringe, remove all of the withdrawable contents if the content is represented as a single dose container, or if the labeling specifies an amount of potency in a given volume of the resultant preparation, use an accurately measured representative portion from each container. For dilute the stock solution with water to 6 to the reference concentration per microgram of colistin base equivalent per milliliter (estimated).

- (2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (c) of that section.
- (3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 10 milligrams colistin base equivalent per milliliter.
- (4) *Safety.* Proceed as directed in § 436.33 of this chapter.
- (5) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.
- (6) *pH.* Proceed as directed in § 436.202 of this chapter, using a 0.5 percent aqueous solution prepared in the following manner: Weigh accurately 0.5 gram of sample and transfer to a 125-milliliter Erlenmeyer flask. Add 10 milliliters of freshly boiled distilled water, stopper, and shake until sample is in solution.

Identity—(i) Infrared. Proceed as directed in § 436.211 of this chapter, using a 1-percent potassium bromide solution prepared as described in paragraph (b)(1) of that section.

(b)(1) of that section. Dissolve 40 milligrams of sample in 1.0 milliliter of hydrochloric acid and add 0.5 milliliter of 0.02N iodine. The color is discharged.

Free colistin. Dissolve 80 milligrams of sample in 3.0 milliliters of distilled water and add 0.05 milliliter of 10 percent w/v solution of silicic acid. It passes the test for colistin if no immediate precipitate is produced.

Heavy metals. Proceed as directed in § 436.208 of this chapter.

19115, May 30, 1974, as amended at 10381, Feb. 20, 1979; 44 FR 22059, 1979.

Colistin sulfate.

Requirements for certification—
standards of identity, strength, and purity. Colistin sulfate is a white to slightly yellow, odorless salt of a kind of colistin or a mixture of two or more such salts. It is dried and dried that:

- (i) Its potency is not less than 500 micrograms of colistin per milligram.
- (ii) It passes the safety test.
- (iii) Its loss on drying is not more than 7.0 percent.
- (iv) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 4.0 and not more than 7.0.
- (v) It gives a positive identity test for colistin.
- (vi) *Labeling.* It shall be labeled in accordance with the requirements of § 431.1 of this chapter.
- (vii) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

- (i) Results of tests and assays on the batch for potency, safety, loss on drying, pH, and identity.
- (ii) Samples required on the batch: 10 packages, each containing approximately 500 milligrams.
- (iii) *Tests and methods of assay—(1) Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dis-

solve an accurately weighed sample in 2 milliliters of sterile distilled water and further dilute with sufficient percent potassium phosphate buffer, pH 6.0 (solution 6), to give a stock solution of convenient concentration. Further dilute the stock solution with solution 6 to the reference concentration of 1.0 microgram of colistin per milliliter (estimated).

(2) *Safety.* Proceed as directed in § 436.33 of this chapter.

(3) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 10 milligrams per milliliter.

(5) *Identity.* To about 20 milligrams of sample, add 2.0 milliliters of pH 7.0 buffer (prepared by adding 29.63 milliliters of 1 N sodium hydroxide to 50 milliliters of 1 M potassium dihydrogen phosphate, adjusting to pH 7.0 if necessary, and diluting to 100 milliliters with distilled water) and 0.2 milliliter of a 0.5 percent aqueous triketohydrindene hydrate solution, and bring to boil. A purple color is produced.

§ 448.23 Cyclosporine.

(a) *Requirements for certification—*
standards of identity, strength, quality, and purity. Cyclosporine is a cyclic polypeptide consisting of 11 amino acids. It is a white or essentially white finely crystalline powder. It is so purified and dried that:

- (i) Its cyclosporine content is not less than 975 micrograms per milligram and not more than 1,020 micrograms per milligram on the anhydrous basis.
- (ii) Its loss on drying is not more than 3.0 percent.
- (iii) Its heavy metals content is not more than 20 parts per million.
- (iv) It passes the identity test.
- (2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.
- (3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(1) Results of tests and assays on the batch for cyclosporine content, loss on drying, heavy metals, and identity.

(ii) Samples, if required by the Director, Center for Drugs and Biologics: 10 packages, each containing approximately 500 milligrams.

(b) *Tests and methods of assay*—(1) *Cyclosporine content.* Proceed as directed in § 436.346 of this chapter, except prepare the working standard and sample solutions as described in cyclosporine content as described in paragraphs (b)(1) (i) and (ii) of this section. A typically suitable column for cyclosporine is a 250-millimeter column having an inside diameter of 4 millimeters packed with octyl silane chemically bonded to totally porous microsilica particles, 5 to 7 microns in diameter.

(i) *Preparation of working standard and sample solutions.*

NOTE: Dissolve working standards and samples immediately before analysis.

(a) *Preparation of working standard solution.* Dissolve an accurately weighed portion of the working standard in ethanol by shaking for at least 15 minutes. If necessary, ultrasonicate until the solution becomes completely clear. Dilute with ethanol to obtain a solution containing 1,000 micrograms of cyclosporine activity per milliliter.

(b) *Preparation of sample solutions.* Prepare all sample solutions as directed for preparation of working standard solutions, except dilute with ethanol to obtain a solution containing 1,000 micrograms of cyclosporine per milliliter (estimated).

(ii) *Calculations.* Calculate the micrograms of cyclosporine per milligram of sample as follows:

$$\frac{\text{Micrograms of cyclosporine per milligram}}{A_s \times P_s \times 100} = A_s \times C_s \times (100 - m)$$

where:

A_s = Area of the cyclosporine peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_s = Area of the cyclosporine peak in the chromatogram of the cyclosporine working standard;

P_s = Cyclosporine activity in the working standard solution in milligrams per milliliter;

C_s = Milligrams of cyclosporine per milligram of sample solution; and

m = Percent loss on drying of the sample.

(2) *Loss on drying.* Proceed as directed in § 436.200(a) of this chapter.

(3) *Heavy metals.* Proceed as directed in § 436.208 of this chapter.

(4) *Identity.* The high-pressure liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section compares qualitatively to that of the cyclosporine working standard.

(Secs. 507, 701 (f) and (g), 52 Stat. 1055-1056, as amended, 59 Stat. 463 as amended (U.S.C. 357, 371 (f) and (g))) [49 FR 22632, May 31, 1984]

§ 448.25 Gramicidin.

(a) *Requirements for certification.*

(1) *Standards of identity, strength, quality, and purity.* Gramicidin is a white, or nearly white, odorless, crystalline compound of a kind of gramicidin or a mixture of two or more compounds. It is so purified and dried that:

(i) It has a potency of not less than 900 micrograms of gramicidin per milligram.

(ii) It passes the safety test.

(iii) Its loss on drying is not more than 3 percent.

(iv) Its residue on ignition is more than 1.0 percent.

(v) Its melting point is not below 229° C after drying in vacuum at 60° for 3 hours.

(vi) When calculated on the anhydrous basis, the difference between the absorptivity value at the maximum occurring at 282 nanometers and the absorptivity value at the minimum occurring at 247 nanometers is 100 percent of the difference obtained with the gramicidin working standard (estimated).

(vii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5(b) of this chapter.

(3) *Requests for certification.* In addition to the requirements of § 431.1 of this chapter, each request shall contain:

(1) Results of tests and assays on the batch for potency, safety, loss

on drying, identity, and crystallinity.

(b) *Tests and methods of assay*—(1) *Samples required of the batch.* 10 packages, each containing approximately 500 milligrams.

(2) *Tests and methods of assay*—(i) *Potency.* Proceed as directed in § 436.206 of this chapter, preparing the sample for assay as follows: Dissolve accurately weighed sample in sufficient alcohol U.S.P. XX to obtain a solution of convenient concentration. Further dilute the stock solution volumetrically with alcohol U.S.P. XX to the reference concentration of 10 micrograms of gramicidin per milliliter (estimated).

(ii) *Safety.* Proceed as directed in § 436.208 of this chapter, except observe for 4 days.

(3) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(4) *Residue on ignition.* Proceed as directed in § 436.207(a) of this chapter.

(5) *Melting point.* Proceed as directed in § 436.209 of this chapter.

(6) *Identity.* Accurately weigh about 10 milligrams of the sample and dilute with alcohol to give a concentration of 0.05 milligram (estimated) of gramicidin per milliliter. Prepare a solution of the gramicidin working standard to contain 0.05 milligram per milliliter in ethyl alcohol. Using a suitable recording spectrophotometer with ultraviolet cells, record the ultraviolet absorbance spectrum of each solution from 220 nanometers to 320 nanometers. The ultraviolet absorbance spectrum of the sample solution should compare qualitatively to that of the working standard solution. Determine the absorptivities of each at the maximum occurring at 282 nanometers and at the minimum occurring at 247 nanometers (the exact position of the maximum and minimum of the gramicidin working standard should be determined for the particular instrument used).

(7) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

(Secs. 507, 701 (f) and (g), 52 Stat. 1055-1056, as amended, 59 Stat. 463 as amended (U.S.C. 357, 371 (f) and (g))) [49 FR 24883, June 21, 1976; 47 FR 23710, June 1, 1982]

(a) *Requirements for certification.*

(1) *Standards of identity, strength, quality, and purity.* Polymyxin B is the sulfate salt of a kind of polymyxin or a mixture of two or more such salts. It is a white to buff-colored powder. It is so purified and dried that:

(i) Its potency is not less than 6 units of polymyxin B per milligram anhydrous basis.

(ii) It passes the safety test.

(iii) Its loss on drying is not more than 7.0 percent.

(iv) Its pH is an aqueous solution containing 5 milligrams per milliliter is not less than 5.0 and not more than 7.5.

(v) It gives positive color identification tests for polymyxin.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, safety, loss on drying, pH, and identity.

(ii) Samples required: 10 packages, each containing approximately 10 milligrams.

(b) *Tests and methods of assay.* *Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: 2.0 milliliters of sterile distilled water to each 5 milligrams of an accurately weighed portion of the sample. Dilute with sufficient 10 percent potassium phosphate buffer, pH 6.0 (sulfite free) to give a stock solution containing 10,000 units of polymyxin B per milliliter (estimated). Further dilute a portion of the stock solution with distilled water to the reference concentration of 10 units of polymyxin B per milliliter (estimated).

(2) *Safety.* Proceed as directed in § 436.33 of this chapter.

(3) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using a solution containing 5 milligrams per milliliter.

Subpart D—Ophthalmic Dosage Forms

§ 448.310 Bacitracin ophthalmic dosage forms.

§ 448.310a [Reserved]

§ 448.310b Bacitracin-neomycin sulfate polymyxin B sulfate ophthalmic dosage forms.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Bacitracin-neomycin sulfate-polymyxin B sulfate ophthalmic ointment contains bacitracin neomycin sulfate, and polymyxin B sulfate in a suitable and harmless ointment base. Each gram contains 500 units of bacitracin, 3.5 milligrams of neomycin, and 10,000 units of polymyxin B. Its bacitracin content is satisfactory if it is not less than 90 percent and not more than 140 percent of the number of units of bacitracin that it is represented to contain. Its neomycin content is satisfactory if it is not less than 90 percent and not more than 140 percent of the number of milligrams of neomycin that it is represented to contain. Its polymyxin B content is satisfactory if it is not less than 90 percent and not more than 140 percent of the number of units of polymyxin B that it is represented to contain. It is sterile. Its moisture content is not more than 0.5 percent. It passes the test for metal particles. The bacitracin used conforms to the standards prescribed by § 448.108(a)(1), except pyrogens, residue on ignition, and heavy metals. The neomycin sulfate used conforms to the standards prescribed by § 444.42a(a)(1) of this chapter, except pyrogens. The polymyxin B sulfate used conforms to the standards prescribed by § 448.30a(a)(1), except pyrogens, residue on ignition, and heavy metals.

- (1) Results of tests and assays on:
 - (a) The bacitracin used in making the batch for potency, safety, loss on drying, pH, and identity.
 - (b) The neomycin sulfate used in making the batch for potency, safety, loss on drying, pH, and identity.
 - (c) The polymyxin B sulfate used in making the batch for potency, safety, loss on drying, pH, and identity.
- (2) The batch for bacitracin content, polymyxin B content, and metal particles.
- (3) Samples required:
 - (a) The bacitracin used in making the batch: 10 packages, each containing approximately 1.0 gram.
 - (b) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 1.0 gram.
 - (c) The polymyxin B sulfate used in making the batch: 10 packages, each containing approximately 1.0 gram.
- (4) The batch:
 - (1) For all tests except sterility: A minimum of 17 immediate containers.
 - (2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(11) *Neomycin content.* Proceed as directed in § 436.105 of this chapter for the sample for assay as follows: Place an accurately weighed representative portion of the sample in a separator funnel containing approximately 50 milliliters of peroxide-free ether. Shake the sample and until homogeneous. Add 20 to 25 milliliters of 0.1M potassium phosphate buffer, pH 8.0 (solution 3), and well. Allow the layers to separate. Remove the buffer layer and the extraction procedure with three more 20- to 25-milliliter portions of solution 3. Combine the extractives in a suitable volumetric flask and dilute to volume with solution 3. Remove an aliquot and dilute with solution 3 to the reference concentration of 1.0 microgram neomycin per milliliter (estimated).

ard in ethanol by shaking for at least 15 minutes. If necessary, ultrasonicate until the solution becomes completely clear. Dilute with ethanol to obtain a solution containing 1 milligram of cyclosporine activity per milliliter.

(b) *Preparation of sample solution.* Using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the concentration of cyclosporine in a given volume of the resultant preparation, remove an accurately measured portion from each container. Dilute with ethanol to obtain a stock solution of 1 milligram of cyclosporine activity per milliliter (estimated).

(11) *Calculations.* Calculate the cyclosporine content of the vial as follows:

$$\text{Milligrams of cyclosporine per milliliter} = \frac{A_1 \times P_2 \times d}{A_2 \times 1,000}$$

where:

A_1 = Area of the cyclosporine peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_2 = Area of the cyclosporine peak in the chromatogram of the cyclosporine working standard;

P_2 = Cyclosporine activity in the cyclosporine working standard solution in micrograms per milliliter; and

d = Dilution factor of the sample.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(2) of that section.

(3) *Bacterial endotoxins.* Proceed as directed in the United States Pharmacopeia XX bacterial endotoxins test. (Sees. 507, 701 (1) and (g), 52 Stat. 1055-1056 as amended, 59 Stat. 463 as amended (21 U.S.C. 357, 371 (1) and (g)))

[49 FR 22683, May 31, 1984]

§ 448.230 Sterile polymyxin B sulfate.

The requirements for certification and the tests and methods of assay for sterile polymyxin B sulfate packaged for dispensing are described in § 448.30a.