UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF TEXAS

BOBBYE JEAN COOPER	§	
	§	
Plaintiff,	§	
	§	
vs.	§	Civil Action No.: 16-593
	§	
WYETH PHARMACEUTICALS, INC., A SUBSIDIARY OF PFIZER, INC., ZYDUS PHARMACEUTICALS (USA) Inc.,	§	
	§	
Defendant	§	

COMPLAINT

Plaintiff BOBBYE JEAN COOPER and complains of Defendants WYETH PHARMACEUTICALS, INC., a subsidiary of PFIZER INC (Wyeth); and ZYDUS PHARMACEUTICALS (USA) Inc. and pleads the following:

I. INTRODUCTION & NATURE OF ACTION

1. Bobbye Jean Cooper was at all times material to this complaint a resident of Austin, Travis County, Texas.

2. Bobbye Jean Cooper was prescribed, purchased, and ingested the drug amiodarone that was designed, marketed or manufactured by Defendants. Her ingestion of amiodarone was the proximate or producing cause or both of severe and debilitating injury to her.

3. Amiodarone ingestion caused Bobbye Jean Cooper to suffer from neurological and physical complications that caused her to no longer be able to care for herself therefore she has had to move into an assisted living facility.

4. Amiodarone was prescribed to Bobby Jean Cooper as treatment for diagnosed non-life-threatening atrial fibrillation. This was an off label prescription for an amiodarone use never approved by FDA.

5. Defendants' unlawful marketing scheme both in the past and now includes a calculated and deceitful marketing campaign. As well, Defendants fail and refuse to take required, timely, and accurate corrective actions, including notice to medical professionals to prevent catastrophic injury and to patient consumers like Bobbye Jean Cooper.

6. Amiodarone has been and is sold under a variety of names, including AMIODARONE HYDROCHLORIDE TABLETS by the Defendants.

7. Wyeth obtained FDA brand name approval of amiodarone, and markets it with the brand name Cordarone®.

8. Zydus Pharmaceuticals (USA) Inc. later received FDA approval to market amiodarone as a generic drug.

9. Defendants unlawfully marketed amiodarone off label for uses never approved by FDA. Bobbye Jean Cooper was prescribed the drug for one of these unlawfully marketed uses.

10. Bobbye Jean Cooper was prescribed amiodarone for an off label use never approved by FDA. She was prescribed amiodarone for atrial fibrillation which is an off label use never approved by FDA.

11. Bobbye Jean Cooper's medical records and the NDC Number of the tablets prescribed and ingested by Bobbye Jean Cooper confirm that she ingested amiodarone manufactured by Zydus Pharmaceuticals (USA) Inc.

12. FDA's approval of amiodarone was for strictly limited usage. It was approved only as a treatment of last resort for life-threatening ventricular fibrillation or ventricular tachycardia that could not be controlled with any other FDA approved option for such specific conditions.

13. Defendants, however, have continuously, and unlawfully marketed amiodarone for off label uses never approved by FDA, particularly for the unapproved use as a treatment for atrial fibrillation.

14. Wyeth's unlawful marketing campaign of amiodarone for off label uses never approved by FDA includes seminars and articles secretly and deceptively controlled by Wyeth, but presented to medical professionals as independent reliable scientific support for the safety and efficacy of unapproved uses.

15. Defendants' lengthy and pervasive unlawful marketing campaign of amiodarone for off label uses never approved by FDA has been effective: It has wrongfully influenced an entire generation of medical professionals.

16. Zydus as a generic manufacture of amiodarone has knowingly benefitted and continues to benefit from Wyeth's marketing misconduct. Zydus engage in its own unlawful marketing of amiodarone for off label uses never approved by FDA.

17. FDA regulates the form and content of prescription drug marketing. Marketing prescription drugs off label for uses never approved by FDA is unlawful. Defendants marketed amiodarone for unapproved uses, particularly for patients with atrial fibrillation. This is unlawful. FDA marketing requirements are meant to ensure that drug companies provide medical professionals with information that enables them to make informed treatment decisions.

18. Defendants failed to test amiodarone as required by FDA. The duty to test proposed drugs and their proposed uses arises under common law as well as federal regulation.

19. The overarching intent of federal prescription drug regulation[1] is protecting patients from drugs that are unproven as safe and effective for specific uses and ensuring that medical professionals are provided the best available reliable scientific data when making patient treatment decisions. This is also the basis for the duty the states impose on drug makers under both their common law and drug regulatory programs.

20. Wyeth was amiodarone's brand maker. It requested FDA's approval of amiodarone for specific uses. It was required to support its approval request with rigorous testing, including demanding clinical trials. This testing duty arises under both state common law and regulatory programs and under federal law.

21. In addition to testing requirements for specific uses, Defendants have a continuing duty to monitor amiodarone after it was approved for marketing. Specifically, Defendants have a continuing duty of pharmacovigilance. Among these requirements, Defendants must seek information relating to negative health effects in patients while on amiodarone and maintain, investigate, evaluate, and formally report these adverse events.

22. 1985 FDA approved Wyeth's application for amiodarone. However, FDA approval was for amiodarone use only as a drug of last resort for patients suffering from documented recurrent life-threatening ventricular fibrillation and ventricular tachycardia that would not respond to any other approved anti-arrhythmic drugs and therapies.[2]

[1] Exhibits "A, B, C" 21 U.S.C. §§331(d), 352(f), and 355.
[2] Exhibit "D" *See* NDA 18-972, Approval Letter, December 24, 1985

23. Flagrantly disregarding the limited use for which FDA approved amiodarone, Wyeth began and continues to unlawfully market amiodarone for off label uses never approved by FDA. For example, Wyeth markets amiodarone as a treatment for non-life-threatening atrial fibrillation. The purpose of this wrongful marketing was to dramatically broaden the patient consumer base for amiodarone and increase Wyeth's revenue and profit.

24. Amiodarone is and always has been a drug associated with extreme risk. Defendants knew this at all times relevant to this complaint. Amiodarone, as evidenced by adverse event reports, among other sources, causes catastrophic injury and death.

25. Upon information and belief, Defendants reaped increased revenue and profit from its unlawful marketing of amiodarone for off label uses never approved by FDA. Amiodarone was approved for a limited patient population. Unlawfully marketing amiodarone for off label uses never approved by FDA, such as atrial fibrillation, increased revenue and profit by exposing millions of patients to amiodarone's serious adverse events from a drug not approved as a treatment for a medical condition they actually had.

26. Upon information and belief, Defendants knew from multiple sources that many, possibly a majority, of their amiodarone prescriptions were written for unlawful off label uses never approved by FDA. Defendants tracked off label prescriptions. They knew their unlawful marketing of amiodarone for off label uses never approved by FDA was successful. That large numbers of prescriptions were written for unapproved uses was well known to Defendants.

27. Defendants concealed their involvement in the unlawful marketing of amiodarone for off label uses never approved by FDA. Defendants conspired together and with others in this scheme.

28. Wyeth actually gained amiodarone FDA approval without double blind randomized testing of any kind. This remains true despite FDA's specific request for this testing.

29. Upon information and belief, Defendants knew from multiple sources that many amiodarone prescriptions were and are written for off-label uses like efforts to treat non-life threatening atrial fibrillation.

30. Defendants' unlawful scheme of marketing amiodarone for off label uses never approved by FDA led medical professionals to believe off label use of amiodarone was appropriate. Yet, Defendants marketed this off label use with full knowledge that the use was not FDA approved, and caused serious injury and death.

31. Because of the years and massive amount of money Defendants spent unlawfully marketing amiodarone for off label uses never approved by FDA, and because of amiodarone's toxicity, FDA requires amiodarone manufacturers to provide each patient with a Medication Guide—a "plain English" description of the dangers of a drug. Defendants failed to provide a Medication Guide that would reach Bobbye Jean Cooper. Bobbye Jean Cooper never received a Medication Guide. Bobbye Jean Cooper's injury was the direct, proximate and producing result of Defendants' misconduct.

II. PARTIES

32. Bobbye Jean Cooper is an 87 year old female who was a resident of Austin, Travis County, Texas during all times material to this complaint.

33. Defendants named in this complaint include all of their predecessor entities and their entire past and present component, subsidiary, and affiliate entities.

34. Defendant Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc is a New Jersey corporation maintaining its principal place of business in Madison, New Jersey. Defendant Wyeth conducts substantial, systematic, continuous, and regular business in Texas. Defendant Wyeth was and is involved amiodarone's design, manufacturing, distribution, marketing, promotion, sale, and labeling in the State of Texas and throughout the United States.

35. Defendant Zydus Pharmaceuticals (USA) Inc. is a New Jersey corporation with a principal place of business in Zydus Pharmaceuticals (USA) Inc.. Defendant Zydus Pharmaceuticals (USA) Inc. conducts substantial, systematic, continuous, and regular business in Texas. Defendant Zydus Pharmaceuticals was and is involved in amiodarone's manufacture, distribution, marketing, promotion, sale, labeling, and design in the State of Texas and throughout the United States.

36. Defendants conduct substantial, systematic, continuous, and regular business in Texas, as well as throughout the United States and were involved in the manufacture, distribution, marketing, promotion, sale, labeling, and design, of amiodarone in the State of Texas and throughout the United States.

37. At all material times, every reference made to any corporate Defendant in this complaint includes predecessors, successors, parents subsidiary, affiliates, and divisions of the corporation.

38. Whenever reference is made to any act, deed, or transaction of Defendants, the allegation means that the corporation engaged in the act, deed, or transaction by or through its officers, directors, agents, employees, or representatives while they were actively engaged in the corporation's management, direction, control, or business affairs. Any Defendant that

is a subsidiary of a foreign parent acted as its parent company's agent for its parent's U.S. business.

III. JURISDICTION AND VENUE

42. Venue is proper pursuant to 28 U.S.C. §1391 because, among other things, a substantial part of the events or omissions giving rise to the claims occurred within the Western District of Texas.

43. Defendants regularly conduct business in the Western District of Texas. Defendants' commercial activities in the Western District of Texas include, but are not limited to, the marketing, sale and distribution of Cordarone®, and its generic bioequivalent, amiodarone.

IV. FACTUAL BACKGROUND

44. All prescription brand name drugs require approval by FDA before the drug may be marketed. Sponsors of proposed new drugs must submit a new drug application (NDA) to the FDA. An NDA must include scientifically reliable information supporting the drug's safety and efficacy for specifically identified uses. FDA approval normally requires rigorous testing, including clinical trials.[3] The NDA must also propose labeling that, among other things, accurately describes the proposed drugs use, warnings, precautions, and adverse reactions.[4]

45. For generic drugs, Congress passed the Drug Price Competition and Patent Term Restoration Act in 1984. This legislation amended the Food, Drug, and Cosmetic Act (FDCA), and is referred to as the Hatch-Waxman Amendments. When the patent for a brand name drug expires, other companies may seek approval to market generic versions of the

[3] Exhibit "C" 21 U.S.C. § 355(a)-(b).
[4] Exhibit "E" 21 C.F.R. § 201.56

brand name drug. The Hatch-Waxman Amendments provided for, in appropriate circumstances, an "abbreviated new drug application" (ANDA) procedure for generic manufacturers.[5] Generic manufacturers, generally, are not required to repeat the clinical trials conducted by name brand manufacturers. ANDA's are primarily approved upon the scientific data that supported FDA approval of name brand drugs. Generic manufacturers are required to provide the information demanded of the brand name manufacturer on all post-marketing events, including, but not limited to, collecting, tracking, and reporting adverse event reports.

46. Defendant Wyeth sponsored approval of a brand name amiodarone.

47. In 1985, Wyeth received FDA approval[6] to market and sell amiodarone under the brand name Cordarone®. FDA approval was granted under a special "needs" approval process. It, therefore, was approved without the rigorous review process demanded of most NDAs. For example, it was approved without double-blind randomized clinical trials.

48. FDA has urged Wyeth to conduct randomized clinical trials. Wyeth has never conducted the trials. FDA approval, therefore, is limited to the unusual "special needs" category.

49. Under the special needs approval, Wyeth's Cordarone® was approved only as a drug of last resort for patients suffering from documented recurrent life-threatening ventricular fibrillation and ventricular tachycardia when these conditions would not respond to other available anti-arrhythmic drugs and therapies. Despite this, Wyeth has consistently and persistently and wrongfully marketed amiodarone for off label uses never approved by FDA.

[5] Exhibit "C" 21 U.S.C. § 355(j)
[6] Exhibit "D" *See* NDA 18-92, Approval Letter, December 24, 1985

50. Wyeth instituted and maintained an active marketing campaign for off label uses never approved by FDA. The campaign was aggressive. In many situations, the off label marketing campaign focused on the use of the drug for first line treatment of non-life-threatening atrial fibrillation. The off label marketing campaign over-played the alleged benefits of off label uses and downplayed the risks of those uses. The off label marketing campaign misrepresented the safety and efficacy of amiodarone for off label uses never approved by FDA. The off label marketing campaign failed to warn medical professionals and patient consumers of the dangers Wyeth knew were associated with the off label uses it was marketing. Wyeth's off label marketing campaign was so pervasive and effective that for an entire generation of physicians, the drug wrongfully became a first line therapy for atrial fibrillation. Wyeth's off label marketing campaign was fraudulent and misleading. This resulted in warning letters from FDA to stop the false and misleading off label marketing of amiodarone.[7] FDA letters noted that it is unlawful for a manufacturer to promote any drug for a use not described in the approved labeling of the drug.[8] Unapproved uses are not supported by NDAs and nor subject to FDA approval scrutiny.

51. Physicians may prescribe drugs for unapproved or off label uses.

52. Pharmaceutical companies may disseminate certain information about off label uses, but such dissemination is stringently limited. For example, the company must submit an NDA seeking approval of proposed off label use; the company must submit materials to the FDA prior to dissemination in unabridged form; and the company must include disclosures that the materials pertain to an unapproved use of the drug, and, if the FDA deems it appropriate, additional objective and scientifically sound information … necessary to provide

[7] Exhibit "F" Warnings by the FDA to Wyeth began as early as 1988.
http://www.mcclatchyde.com/2003/11/04/28118/fda-oversight-of-off-label-drug.html
[8] Exhibits "A,B,C" *See* 21 U.S.C. §§ 331(d), 352(f), and 355

objectivity and balance. The dissemination of information in violation of these provisions violates the Food, Drug and Cosmetic Act (FDCA)[9]. This law also requires pharmaceutical companies to furnish federal regulators with advance copies of the information they disseminate. Any deviation from these requirements violates FDA regulations

53. In 2008, Defendant Zydus Pharmaceuticals (USA) Inc. received approval for the manufacture, marketing, sale and distribution of the generic formulation of amiodarone. As with all generic bioequivalent approvals, FDA required Zydus Pharmaceuticals (USA) Inc. to provide patients prescribed the drug all FDA approved labels, warnings and medication guides with information exactly as required of the brand formulation manufacturer.[10]

54. Zydus Pharmaceuticals (USA) Inc. took advantage of, or "free rode," Wyeth's pervasive and wrongful off label marketing campaign. Zydus Pharmaceuticals (USA) Inc. was subject to the same advertising, marketing, and promotional requirements and restrictions set forth by FDA in its special needs approval of Wyeth's Cordarone®. Zydus Pharmaceuticals (USA) Inc. was required by FDA to provide patients prescribed amiodarone with all FDA approved labels, warnings, and medication guides. Zydus Pharmaceuticals (USA) Inc. was required to provide this information exactly as FDA required Wyeth, the brand manufacturer, to provide the information.[11]

55. As with all generic bioequivalent approvals, Zydus Pharmaceuticals (USA) Inc. was required by the FDA to provide patients prescribed amiodarone with all FDA approved labels, warnings and Medication Guides with information exactly as required of the brand formulation manufacturer, Wyeth, by FDA, and as updated as directed by the FDA.[12] Zydus

[9] Exhibit "A" 21 U.S.C. § 331(z)
[10] Exhibit "C" *See* 21 U.S.C. § 355(j)(2)(A)(v); § 355(j)(4)(G).
[11] Exhibit "C" *See* 21 U.S.C. § 355(j)(2)(A)(v); § 355(j)(4)(G).
[12] Exhibit "C" *See* 21 U.S.C. § 355(j)(2)(A)(v); § 355(j)(4)(G).

Pharmaceuticals (USA) Inc. took advantage of the pervasive promotional activities of Wyeth. Zydus Pharmaceuticals (USA) Inc.' generic version of the drug directly benefited from the decades of marketing of amiodarone for off label uses by Wyeth as well as their own marketing activities.

56. Prior to being prescribed amiodarone, Bobbye Jean Cooper was diagnosed with atrial fibrillation not deemed life threatening. Amiodarone was never an approved drug for this condition.

57. Dr. David Morris prescribed Bobbye Jean Cooper a course of amiodarone from March 11, 2016 through April 4, 2016; 200 mg tablets three times a day for treatment of non-life threatening atrial fibrillation The physician prescribed amiodarone off label for this unapproved use as a result of the long term and pervasive promotional activities of Wyeth, and the continuation of this wrongful off label promotion by Zydus Pharmaceuticals (USA) Inc.

58. Bobbye Jean Cooper filled the prescription and ingested amiodarone as instructed.

59. Dr. Morris was a victim of Wyeth's long term and successful off label marketing campaign as well as Zydus Pharmaceuticals (USA) Inc.' marketing that, among other wrongful acts, failed to point out the details and dangers of amiodarone toxicity related to off label prescription of amiodarone for atrial fibrillation. Accurate information would have prevented Bobbye Jean Cooper from ingesting the drug.

60. Bobbye Jean Cooper was not aware that amiodarone was prescribed off label.

61. Bobbye Jean Cooper never received the required Medication Guide from Zydus Pharmaceuticals (USA) Inc. for the prescription she filled at the Tarrytown Pharmacy in Austin, Texas. Medication Guides were not provided by the Zydus Pharmaceuticals (USA)

Inc. for distribution to Bobbye Jean Cooper with her prescription. She, therefore, received and ingested a mislabeled drug.

62. Treatment of atrial fibrillation was never an FDA approved use of amiodarone. Bobbye Jean Cooper's prescription was off label use and without the benefit of the FDA mandated Medication Guide. Bobbye Jean was unaware of the dangers she faced from the drug that caused her injury.

63. On information from the prescription bottle, Bobbye Jean Cooper was sold and ingested amiodarone manufactured, marketed and distributed by Zydus Pharmaceuticals (USA) Inc. It was the generic version of Wyeth's Cordarone®. This off label prescription and distribution of amiodarone to treat non-life threatening atrial fibrillation, also a direct result of the long term promotional efforts of Wyeth and the continuing sales efforts of Zydus Pharmaceuticals (USA) Inc., without the required Medication Guide, was a producing and proximate cause of Bobbye Jean Cooper's injuries from amiodarone toxicity.

64. Bobbye Jean was not aware that her use of the medication was an off label use never approved by FDA. Bobbye Jean never received the required Medication Guide from Defendant Zydus Pharmaceuticals (USA) Inc. for the prescription she filled at the pharmacy.

65. Bobbye Jean Cooper was not provided the Medication Guide[13] or the appropriate and up to date warning labels from Zydus Pharmaceuticals (USA) Inc. that was required to be given directly to her outside of her interaction with Dr. Morris to warn her of the serious and life threatening side effects of amiodarone. Zydus Pharmaceuticals (USA) Inc. was responsible by federal regulation for ensuring that the appropriate warning labels and

[13] Exhibit "G" The FDA requires that Medication Guides be issued with certain prescribed drugs and biological products when the Agency determines that certain information is necessary to prevent serious adverse effects; patient decision-making should be informed by information about a known serious side effect with a product, or patient adherence to directions for the use of a product are essential to its effectiveness. http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm

Medication Guides were provided to Bobbye Jean Cooper. Had the Medication Guide been provided by Zydus Pharmaceuticals (USA) Inc. to the distributor or her pharmacist for distribution to Bobbye Jean Cooper as required by FDA regulations, Bobbye Jean would have been aware of the serious side effects that would lead to her injury as well as other risks associated with amiodarone. Bobbye Jean would not have taken amiodarone had she received the required Medication Guide.

66. The serious side effects of amiodarone are outlined in the Medication Guide, some of which Bobbye Jean Cooper experienced after taking amiodarone, including tiredness, weakness, nervousness, irritability, restlessness, decreased concentration and depression as well as neurological and physical complaints. [14]

67. Because her distributor and pharmacist were not provided a Medication Guide to give her by the Defendants, Bobbye Jean did not know that amiodarone "should only be used in adults with life-threatening heartbeat problems called ventricular arrhythmias" and, even then, only when "other treatments did not work or were not tolerated." [15] She did not know that any other use such as the use for his atrial fibrillation was considered to be off label and he did not know of the corresponding dangers associated with such uses. Bobbye Jean Cooper did not know "the medicine stays in your body for months after treatment is stopped." [16] The effects of amiodarone are extremely long lasting.

68. Amiodarone is fat-soluble, and tends to concentrate in tissues, including fat, muscle, liver, lungs, and skin and confers a high volume of distribution and a long half-life; the amount of time it takes for one-half of an administered drug to be lost through biological processes (metabolism and elimination). Because of this long half-life, amiodarone's

[14] Exhibit "H" Medication Guide for amiodarone HCl.
[15] Exhibit "H" Medication Guide for amiodarone HCl.
[16] Exhibit "H" Medication Guide for amiodarone HCl.

dangerous properties continue to cause injuries in patients such as Bobbye Jean long after she ceased using the drug, including, serious pulmonary injuries. This information was unknown to her. Defendants never provided the Medication Guide to the distributor and pharmacist.

69. Each manufacturer who ships a container of an FDA approved drug product for which a Medication Guide is required is responsible for ensuring that Medication Guides are available for distribution to patients.[17] Zydus Pharmaceuticals (USA) Inc. is a manufacturer of amiodarone as defined by the FDA and are required to provide the Medication Guides to the distributors so that the distributors can provide the Medication Guides to pharmacists who then can provide Medication Guides directly to the patient. The FDA has recognized that "it is important that patients receive appropriate risk information in the form of Medication Guides in order to make informed decisions about certain prescribed medications." The Medication Guides are to specifically provide information directly to the patient outside of the interaction with the physician. It is important to note that the FDA has mandated that the warnings included in the Medication Guides go directly to the distributor and via the distributor and pharmacists directly to the patient as an important notification distributed outside and in addition to any warning or information that is provided by the physician. Drugs identified by the FDA for the Medication Guide procedure are significantly dangerous to such a degree that the FDA desires a warning outside of information provided directly by the physician. Failure to provide the Medication Guide results in the distribution of a mislabeled and illegal drug.

70. The National Consumer Pharmacy Association has also identified the failure of manufacturers to ensure the distribution of Medication Guides to distributors and thus to the patients as a significant safety issue and called on FDA to "enforce current FDA MedGuide

[17] Exhibit "I" *See* 21 C.F.R. § 208.24

regulations holding manufacturers accountable for providing Medication Guides in sufficient number or the means to produce Medication Guides in sufficient number, to permit the authorized dispenser to provide a Medication Guide to each patient who receives a prescription for the drug product."[18] Bobbye Jean did not receive a Medication Guide, because Zydus Pharmaceuticals (USA) Inc. did not provide the Medication Guide to the distributor.

71. In April of 2016, Bobbye Jean Cooper began to experience symptoms outlined in the Medication Guide, including, tiredness, weakness, nervousness, irritability, restlessness, decreased concentration, depression, and other neurological and physical complaints. The amiodarone was discontinued and gradually there was some but not total improvement in her symptoms. Prior to her use of the amiodarone she was able to live and care for herself but since experiencing significant adverse events to amiodarone toxicity she no longer can care for herself and has had to move into an assistive living facility.

A. Cordarone®, Concealment, And The Off-Label Marketing By Defendant Wyeth

72. As noted above, on or about December 24, 1985, Wyeth launched Cordarone® into the United States' stream of commerce. Wyeth received approval for Cordarone® from the FDA only as a drug of last resort for patients suffering from documented recurrent life-threatening ventricular fibrillation and ventricular tachycardia; and further, only when those conditions would not respond to other available anti-arrhythmic drugs and therapies. The bioequivalents manufactured by Zydus Pharmaceuticals (USA) Inc. received approval for the manufacture, marketing, sale and distribution of the generic formulation amiodarone hydrochloride in 2008 under the same approval guidelines by the FDA as for Cordarone®.

[18] Exhibit "J" Use of Medication Guides to Distribute Drug Risk Information to Patients, Colleen Brennan, RPh; Bryan Ziegler, PharmD, MBA

73. The FDA's early specific enforcement actions regarding the marketing and labeling of the drug Cordarone®, include:

a. On or about October 7, 1986: label revision;
b. On or about May 15, 1987: label revision;
c. On or about August 7, 1987: package change;
d. On or about October 28, 1987: manufacturing changes;
e. On or about June 29, 1988: label revision;
f. On or about September 14, 1988: label revision;
g. On or about December 13 1988: package change;
h. On or about February 2, 1989: label revision;
i. On or about July 28, 1989: formulation revision;
j. On or about August 9, 1990: label revision;
k. On or about August 9, 1990: manufacturing change;
l. On or about April 14, 1994: label revision;
m. On or about October 15, 1995: label revision;
n. On or about June 15, 1998: label revision;
o. On or about January 5, 1999: label revision;
p. On or about October 8, 1999: label revision;
q. On or about December 18, 1999: label revision;
r. On or about September 20, 2002: control supplement;
s. On or about December 18, 2002: label revision;
t. On or about April 30, 2003: label revision;
u. On or about May 6, 2003: label revision; and
v. On or about May 21, 2004: label revision.

74. On or about December 15, 1989, and subsequently in 1992, 1998, and thereafter, the FDA sent violation communications to Wyeth regarding the FDA's determination that Wyeth had violated the Act and its implementing regulation by, *inter alia*, disseminating false and misleading materials to physicians and the public without adequate risk information concerning the use of Cordarone®. Wyeth misrepresented Cordarone's® indications and usage, efficacy, risks, and benefits. Further, Wyeth intentionally failed to submit marketing materials to the FDA in violation of the Act.

75. Upon information and belief, in May of 1995, the Australian Government's Therapeutic Goods Administration (that country's counterpart to the U.S. FDA), issued an Australian Adverse Drug Reactions Bulletin, emphasizing that amiodarone was appropriate

only for use in the treatment of ventricular and supraventricular arrhythmias. Notably, this Bulletin highlighted that "the drug [Amiodarone] is known to have multiple adverse effects, which can involve most organ systems," and again stressed that "Amiodarone is only to be used in patients with serious arrhythmias where there is no safer drug therapy."

76. Upon information and belief, on or about April 29, 1996, the FDA required Wyeth to change its labeling, warnings, and packaging for Cordarone®; specifically, adding new warnings or revising minimalist warnings regarding the following:

a. Carcinogenesis;
b. Mutagenesis;
c. Impairment of fertility, pregnancy; and
d. Neonatal hypo- or hyperthyroidism.

77. Upon information and belief, the severity of catastrophic adverse reactions, including death, led Wyeth to discontinue production and distribution of Cordarone® in Canada on or about September 10, 1996.

78. Upon information and belief, on or about February 11, 1997, the FDA issued a warning letter to Wyeth regarding Cordarone's® understated or incorrect labeling and warnings based on the FDA's medical research. Thereafter, on or about April 16, 1997, Wyeth changed its labeling, warnings, and packaging for Cordarone®; specifically adding new warnings or revising minimalist warnings regarding the following:

a. Loss of vision;
b. Impairment of vision, including optic neuritis, optic neuropathy, corneal lesions, lens opacities, optic disk damage, papilledema, retinal hemorrhage and degeneration, photophobia;
c. Liver injury;
d. Pregnancy;
e. Adult respiratory distress syndrome;
f. Angioedema; and mortality

79. Upon information and belief, in 1998 the FDA issued a Written Request for Pediatric Studies under Section 505A of the Act to Wyeth regarding Cordarone®. Upon information and belief, the basis of this request was that insufficient tests, surveys, and studies had been conducted regarding Cordarone® consumption by pediatric patients, although there was knowledge by Defendants and other drug manufacturers and in the medical community that off label use of Cordarone® in pediatric patients was becoming common.

80. Upon information and belief, in 1998 the FDA issued a letter to Wyeth requiring it to change its labeling, warnings, and packaging for Cordarone®; specifically, adding new warnings or revising minimalist warnings regarding the following:

a. Mortality (based upon the European Infarct Amiodarone Trial and Canadian Myocardial Infarct Trial);
b. Precautions regarding volatile anesthetic agents for Amiodarone users undergoing surgery;
c. Carcinogenesis;
d. Mutagenesis;
e. Impairment of fertility, pregnancy; and
f. Neonatal hypo- or hyperthyroidism.

81. Upon information and belief, Wyeth's sales and promotional practices for Cordarone®, included a December 6-10, 1998, Wyeth sponsored CME for the 33rd Midyear Clinical Meeting of the American Society of Health-System Pharmacists. This CME was for healthcare providers, including pharmacists, as part of Wyeth's ongoing promotion of Cordarone® for off label purposes. As part of the CME, Wyeth produced and distributed to attendees, a 68-page official looking, "peer review appearing" magazine, "The Pharmacist Reporter (July 199, Vol.4, No.5)." This publication was actually a promotional bulletin highlighting Wyeth's goal for Cordarone®: increased off label use. Among the topics

addressed in various articles in "The Pharmacist Reporter," several of which appear to soften, downplay, and minimize Cordarone's® devastating side effects, were the following:

a. "An Aggressive Treatment Strategy for Atrial Fibrillation";
b. "Use of Amiodarone in Patients Undergoing Cardiothoracic Surgery", and
c. "A Possible New Standard of Care for Prehospital Cardiac Arrest."

82. On or about October 8, 1999, the FDA issued a letter to Wyeth requiring Defendant Wyeth to change its labeling, warnings, and packaging for Cordarone®; specifically, adding new warnings or revising minimalist warnings regarding the following:

a. Clinical pharmacology and pharmokinetics, in that food consumption increases Cordarone® absorption rate;
b. Geriatric use, whereby clinical studies of Cordarone® in persons 65 an older had not been conducted; and
c. Dosage and administration, in that food consumption must be addressed in dosing and loading doses are to be used.

83. On or about January 12, 1999, the FDA issued a letter to Wyeth requiring Defendant Wyeth to change its labeling, warnings, and packaging for Cordarone®; specifically, adding new warnings or revising minimalist warnings regarding geriatric use, whereby clinical studies of amiodarone in persons 65 and older had not been conducted.

84. On or about February 12, 1999, the FDA issued a letter to Wyeth requiring Defendant to change its labeling, warnings, and packaging for Cordarone®; specifically adding new warnings and revising minimalist warnings regarding the effects of food consumption on dosage and administration.

85. Defendant Wyeth was affected by the February of 2002 Australian Government's Therapeutic Goods Administration (TGA) issuance of an Australian Adverse Drug Reactions Bulletin, alerting healthcare professionals in that county that numerous adverse medical events associated with Cordarone® had been reported to the TGA in 2002 and 2001,

including Cordarone® induced pulmonary toxicity and deaths. The TGA warning contained the following important information for healthcare professionals:

> Although commonly insidious in onset, amiodarone—induced pulmonary toxicity may develop rapidly. The lowest effective dose should be used, and patients should be instructed to report any dyspnea or non-productive cough. Amiodarone also has other toxicities including hepatotoxicity which can cause cirrhosis and hepatic failure, cardiovascular effects including bradycardia and tachycardia, skin reactions including photosensitivity and discoloration, neurotoxicity including ataxia and peripheral neuropathy, as well as both corneal deposits and hyper- and hypothyroidism.

86. On or about December 18, 2002, the FDA issued a letter to Wyeth requiring Wyeth to change its labeling, warnings, and packaging for Cordarone®; specifically, adding new warnings or revising minimalist warnings regarding adverse drug interactions with immunosuppressant static drugs, resulting in rhabdomyolysis.

87. On or about December 19, 2002, the FDA issued a warning letter to Wyeth requiring Defendant to correct understated warnings and/or issue new warnings regarding the following:

a. Acute onset (days to weeks) of pulmonary toxicity;
b. Patients having preexisting pulmonary disease have poorer prognosis if pulmonary toxicity develops; and

c. Post-marketing reports include possible fatal respiratory disorders (including distress, failure, arrest, ARDS, fever, dyspnea, cough, hemoptysis, wheezing, hypoxia, and pulmonary infiltrates).

88. In 2003, the FDA issued a warning letter to Wyeth, requiring Defendant Wyeth to change its labeling, warnings, and packaging for Cordarone®; specifically, adding new warnings or revising minimalist warnings regarding the following:

a. Worsened arrhythmia;
b. Thyroid abnormalities;
c. Drug interactions (protease inhibitors histamine antagonists, immunosuppressives, antibiotics, cardiovasculars, anti-arrhythmics, anti-hypertensives, anticoagulants);

d. Other substances (grapefruit juice, herbal supplements) interactions;
e. Electrolyte disturbances; and
f. Nursing mothers passing the drug to newborns through breast milk.

89. Optic neuropathy is an under reported adverse side effect of Cordarone®.

90. It was known to Wyeth that Cordarone® use had resulted in vision loss and permanent blindness.

91. Wyeth had previously been forced by the Canadian Government to change the drug's labeling in Canada.

92. In addition, upon information and belief, Defendant Wyeth's pharmaceutical sales and marketing directors encouraged their respective sales representatives to visit physicians' offices throughout the United States to promote and over promote the drug for off-label use, such as atrial fibrillation. Upon information and belief, Wyeth's realized more than Three Billion ($3,000,000,000) in sales for "off-label" uses of Cordarone®.

93. To date, despite changing the warnings and labeling for Cordarone® multiple times over the past 25 years and the requirement for the distribution of Medication Guides to all patients, and knowing of numerous catastrophic injuries caused by Cordarone®, Wyeth continues to understate the drug's nature and adverse risks of catastrophic injury, pulmonary injury and death.

94. Defendant Wyeth was on notice, by no later than 1998, that sever damage to the lungs were side effects of the ingestion of Cordarone® which can cause permanent injury and death.

95. In 2003, the FDA sent violation communications to Defendant Wyeth regarding the FDA's determination that Defendants had violated the Act and its implementing regulation by, *inter alia*, disseminating false and misleading materials to physicians and the

public without adequate risk information concerning the use of Cordarone® by children and pregnant women. Thereafter, these Defendants notified physicians to stop prescribing Cordarone® to children and pregnant women because of the serious risk of permanent injuries.

96. Defendant Wyeth misrepresented Cordarone's® indications and usage efficacy, risks and benefits. Further, Defendant Wyeth intentionally failed to submit marketing materials to the FDA in violation of the Act.

97. At all material times, Defendant Wyeth willfully failed and refused to actively and affirmatively monitor Cordarone's® off label unapproved uses as such uses caused catastrophic injuries and death. Defendant Wyeth, however, continued to promote Cordarone® for unapproved uses. Such promotion had direct beneficial results for generic Defendants Zydus Pharmaceuticals (USA) Inc. as well.

B. Facts Common To All Defendants

98. At all material times, Defendants, respectively, jointly and severally, have had actual or constructive knowledge that Cordarone® and amiodarone cause and contribute to severe and disabling medical conditions and death, including, without limitation, the following: pulmonary toxicity, pulmonary fibrosis, hepatic damage and failure, neurotoxicity, neonatal hyperthyroidism, birth defects, optic neuritis, toxic optic neuropathy, blindness, peripheral neuropathy, heart damage and failure, hypotension, serious exacerbation of arrhythmias, and congestive heart failure.

99. Upon information and belief, Defendants, respectively, jointly and severally, have received information concerning more than one thousand deaths resulting from the use of Cordarone®/amiodarone.

100. Defendants, respectively, jointly and severally, have received information concerning cases of pulmonary toxicity, pulmonary fibrosis, and lung damage such as that experienced by Bobbye Jean Cooper.

101. Healthcare providers, as well as patient-consumers reported these events, upon information and belief, directly to the company.

102. In addition to these direct notices of adverse events, the FDA had, and continues to have, in effect, an adverse reaction surveillance system for all regulated drugs, including amiodarone, called the Adverse Event Reporting System (AERS).

103. At all material times, Defendants failed to disclose to the FDA, healthcare professionals, consumers, or Bobbye Jean Cooper, the information they possessed concerning the incidents and actual adverse medical events, injuries, and deaths suffered by Cordarone®/amiodarone users. Instead, upon information and belief, these Defendants actively promoted, or piggy-backed the promotional efforts of Wyeth for off label unapproved uses as described herein through various means, including, but not limited to, the following:

a. Direct-to-physician and direct-to-pharmacist promotion through sales representatives;

b. Promotion through funding and manipulation of so-called "educators" who organized and arranged continuing medical education (CME) courses for physicians and pharmacists;

c. Formulation of unlawful conspiracies with certain medical marketing and medical "education" entities to promote – without appearing to promote – off-label uses;

d. Sponsorship and funding of production of CME materials;

e. Cultivation and development of so-called "opinion leaders" in local medical communities and support for the careers and research of those physicians, pharmacists, and researches who advocate off label uses;

f. Sponsorship of journal supplements and symposia on off label uses for Cordarone®; placing (through sponsorship of limited trials, studies, and surveys) of medical literature databases showing positive effects already established with the twin purposes of overwhelming any independent study showing negative effects of different risk factors, and causing earnest but time-crunched physicians to be impressed with the sheer quantity of favorable (but redundant) studies on MedLine, or medical library, search;

g. Media advertisements and brochures, some of which were disguised as "educational materials", and

h. Various other forms of marketing and promotion.

104. Upon information and belief, in accepting the benefits of brand innovator Wyeth's efforts in promoting "off-label" uses of Cordarone® by sponsoring CME conferences and materials, journal supplements, redundant trials, and the work and careers of favorably disposed opinion leaders, Defendants would sometimes escape disclosure for any role at all in the presentation of its desired view.

105. Additionally, upon information and belief, Zydus Pharmaceuticals (USA) Inc. and/or their agents, pharmaceutical sales representatives, and materials and sources actively promoted their generic amiodarone in the stream of commerce for the off label uses promoted by Wyeth.

106. At other times, Defendants would be disclosed or described as merely providing "unrestricted educational grant[s]" for seminars when in fact that grant was premised on an understanding about the content or Defendants otherwise exercised influence over it.

107. At all material times, despite FDA warnings and thousands of adverse patient experiences, Defendants continued their fraudulent marketing, promotional, and sales practices from 1999 through the present date.

108. At all material times, Defendants, respectively, jointly and severally, concealed information about catastrophic injuries and death, and thousands of serious adverse medical events from the FDA, healthcare professionals, and consumers including Bobbye Jean Cooper.

109. At all material times, amiodarone, manufactured or supplied by Defendants was and is unaccompanied by proper warnings regarding all possible adverse side effects and comparative severity and duration of such adverse effects. The warnings given did not and do not accurately reflect the severity or duration of the adverse side effects or the true potential or likelihood or rate of the side effects. This is particularly so with regard to off label use.

110. At all material times, Defendants failed to warn of material facts regarding the safety and efficacy of amiodarone, such that this drug would likely never have been approved for marketed off label uses.

111. At all material times, Wyeth failed to perform adequate testing. Adequate testing would have shown that amiodarone possessed serious potential side effects, and required warnings that accurately and fully reflected the symptoms, scope, and severity of the side effects This is particularly true for wrongfully promoted off label use.

112. For example, although Defendants know that the majority of patients consuming amiodarone are older, including those aged 55 and over such as Bobbye Jean Cooper, Wyeth has failed and refused to conduct testing, studies, surveys, or report the results of any such studies in this age group.

113. At all material times, amiodarone manufactured, distributed, or supplied by Defendants was defective due to inadequate post-marketing warning and instruction, because, after Defendants knew or should have known of the risk of injury from amiodarone,

especially when used off label, Defendants failed to provide adequate and required warnings to physicians, users or consumers of amiodarone, and continued to aggressively market it for off-label use.

114. At all material times, while Defendants, respectively, jointly, and severally, concealed adverse event information, they simultaneously engaged in a massive and fraudulent marketing and promotional scheme in which they aggressively and fraudulently promoted amiodarone for uses never authorized by the FDA. In fact, Defendants marketed, promoted, and "pushed" amiodarone, not as a drug of last resort, but as a drug suitable as an initial therapy and to treat non-life-threatening heart conditions.

115. At all material times, Defendants respectively, jointly and severally, also promoted amiodarone for heart conditions less severe than life-threatening ventricular arrhythmia.

116. Defendants engaged in a conspiracy of silence regarding off label use, choosing to market and promote the drug for off label use, and then feigning ignorance before the FDA, healthcare providers, and consumers. They failed and refused to conduct thorough testing on the side effects, despite knowing that their scheme to promote the drug for off label use had been, and continues to be, successful.

117. Defendants have engaged in this calculated and coordinated silence despite their knowledge of the growing public acceptance of misinformation and misrepresentations regarding both the safety and efficacy of the use of amiodarone, and did so because the prospect of significant future profits outweighed their concern regarding health and safety issues, all to the significant detriment for the public and Bobbye Jean Cooper.

118. At all material times, Defendants' affirmative misrepresentations and omissions have so infected the market in the United States that physicians and consumers relied on Defendants' fraud to the detriment of their patients and themselves.

119. Under increased FDA scrutiny and mandates, Wyeth has been forced to correct and change their warning labels, and add new warnings, for Cordarone® The "new" warnings are for adverse side effects about which Defendants knew long before being required to make such changes.

120. Nevertheless, at all material times, the warnings for amiodarone, in effect during the relevant time period were vague, incomplete, and/or otherwise wholly inadequate, both substantively and graphically, to alert prescribing physicians, pharmacist, consumer patients and Bobbye Jean Cooper of the actual risks associated with this drug.

121. At all material times, Defendants' deception, concealment, and fraudulent marketing and promotion has been so pervasive throughout the United States, that prescribing physicians and consumer patients have during the relevant time period and still believe that amiodarone, is an acceptable initial, secondary, or otherwise early-stage anti-arrhythmic intervention. These deceptive off label marketing techniques serve (and continue to serve) Defendants in several ways, including: (1) instilling Defendants' desired view about the drug's off label use among healthcare providers; (2) evading legal ramifications of unlawful promotional activities by concealing their actual involvement in these activities; and (3) boosting Defendants' profits for the drug.

122. At all material times, Defendants, and each of them respectively, jointly, and severally, owed a duty to the healthcare providers, consumer patients, and Bobbye Jean Cooper, to engage in honest and non-deceptive practices; exercise due care in the design,

testing, manufacture, marketing, promotion, sale and distribution of amiodarone; to provide a reasonably safe and non-defective drug; to provide adequate and appropriate warnings for the drug; to comply with federal guidelines, rules, and regulations; and sell and distribute the drug in accordance with FDA restrictions.

123. At all material times, Defendants marketed amiodarone, as having approval, characteristics, uses, and benefits that the drug did not have.

124. At all material times, Defendants respectively, jointly and severally, did design, create, test, develop, label, sterilize, package, manufacture, market, promote, advertise, distribute, sell, warn, and/or otherwise caused the product to be placed into the stream of commerce, and ultimately to be ingested by Bobbye Jean Cooper.

125. At all material times, Defendants willfully failed and refused to actively and affirmatively monitor amiodarone's off label unapproved uses. Those uses have caused catastrophic injuries and death. Defendants, however, continued to sell and market amiodarone for unapproved uses.

126. At all material times, Defendants, respectively, jointly and severally, engaged in a continuing course of fraud, concealment, material nondisclosure and omission, upon patient consumers and medical professionals that prevented them from knowing or having reason to know of Defendant's misconduct.

C. Amiodarone Did not Undergo The Rigorous FDA Approval Process Required for Federal Preemption

127. As noted above, on or about December 24, 1985, Wyeth launched amiodarone into the United States' stream of commerce under the brand name Cordarone®. Wyeth received approval from the FDA for amiodarone only as a drug of last resort for patients suffering from documented recurrent life-threatening ventricular fibrillation and ventricular

tachycardia; and further, only when these conditions would not respond to other available anti-arrhythmic drugs and therapies. Furthermore, despite repeated requests by the FDA at the outset of the review process and throughout the history of the drug, neither Wyeth nor the amiodarone generic drug manufactures have submitted the drug to the rigorous randomized clinical trials required for FDA drug approval.

128. As a result, unlike virtually every other prescription drug in modern history, amiodarone became FDA approved without rigorous, FDA sanctioned randomized clinical trials. The legal reasons for preemption applied to drug litigation for FDA approved drugs are not present in amiodarone. Amiodarone has never been subjected to double blind testing as mandated by the FDA.

129. Amiodarone has been determined to affect many different organs in many ways. First, the drug takes many weeks to achieve the maximum effectiveness. Amiodarone is literally "stored" in most of the tissues of the body and to "load" the body with the drug all the tissues need to be saturated. Therefore, the typical loading regimen of amiodarone is to use extremely large doses of the drug for the first week to two weeks then to taper the dosage over the next month. It is not unusual to give a patient 1200 to 1600 mg dose a day when starting the drug and to maintain the patient on as little as 100 to 200 mg per day on a chronic basis.

130. Amiodarone leaves the body very slowly. The drug is not excreted like most drugs through the liver or kidney but is only lost when amiodarone containing cells such as skin cells or cells from the GI tract are lost. Therefore, even when it is decided that the patient needs to stop taking amiodarone the drug remains in the system in measurable quantities for months and even years.

131. The drug is stored in many different types of tissues, and therefore, it can cause side effects that affect many different types of organs. Some of the side effects take months and years to develop. Constant diligence is needed.

132. Amiodarone causes many horrific side effects that have resulted in its restricted use in the United States including; causing blindness, it causes deposits to form on the cornea of the eyes, a condition in virtually everyone who takes the drug; amiodarone causes a very disfiguring blue-grey discoloration of the skin, generally in areas of exposure to the sun; amiodarone often sensitized the skin to sunlight so that even trivial exposure results in severe sunburns; amiodarone causes hypothyroidism-low thyroidism, - a condition relatively easy to treat with thyroid medication. Some patients develop hyperthyroidism-high thyroid, which is more dangerous and more difficult to treat. Amiodarone can cause liver toxicity; therefore, liver enzymes need to be monitored periodically. Amiodarone can cause severe gastric reflux, caused by a paralysis of the sphincter at the end of the esophagus.

133. The most serious side effect of amiodarone and the one requiring the patient Medication Guide is pulmonary toxicity-lung disease. Amiodarone produces two types of lung disease-first, acute pulmonary syndrome, which looks and acts like typical pneumonia, with a sudden onset of cough and shortness of breath, a condition that rapidly improves once the amiodarone is stopped. The second type is more dangerous. This condition involves a gradual, almost unnoticeable, stiffening of the lungs that both the doctor and patient overlook until finally severe irreversible lung damage is done.

134. Amiodarone never underwent the rigorous clinical randomized trials all other FDA approved drugs other than a few “grandfathered” drugs with long market histories have undergone. Despite repeated requests, demands and even threats from the FDA, Defendants

admit FDA approval was granted without the type of clinical trials that would show amiodarone's risks or the benefits. Despite the economic argument that the patent has expired, or that the costs of testing is too high to justify the investment, amiodarone continues to generate enormous revenues for the drug manufacturers without the public having the protection of FDA required scrutiny.

135. The only trials amiodarone underwent were non-scientific, reporting of a combination of various patient results combined to obtain statistical data that is neither randomized or reliable and which did not even provide the statistical data that has been determined by the FDA to be accurate for the drug and required in the black box labeling of the product. Obviously, this combination of reporting of various patients was non-scientific and cannot serve as the basis for a claim of preemption.

136. Without rigorous, scientific, clinical trials and randomized testing approved by the FDA the reasons for FDA preemption do not exist and cannot be sustained. Since the manufacturers will not undergo FDA approved testing they cannot use the FDA approval process as a shield from liability when sued. None of the reasons articulated by the United States Supreme Court for the protection preemption provides are present with amiodarone. None of the costs benefits analysis is present. In addition, none of the regulatory analysis argument and certainly no Federalism argument are present to support preemption.

137. This is not to say the FDA completely disregarded its regulatory or enforcement powers regarding amiodarone. While no testing justifying preemption was ever performed, when the statistical evidence of the dangers of amiodarone and its many side effects became known, the FDA repeatedly amended the labeling requirements for amiodarone, mostly resulting from public pressure and enacted a requirement that the drug manufacturer directly

provide the patient a FDA approved "Medication Guide" by ensuring distribution of the Medications Guides to the distributors and then to the patient along with the drug. Due to the failure to conduct required randomized clinical testing by the Defendants, Plaintiff is not preempted from claiming the Defendants illegally marketed the product for off-label use, and is not preempted from claiming that the product itself is unreasonably dangerous as it was packaged, marketed, designed, manufactured and sold. Most importantly, Plaintiff is not preempted from claiming Defendants failed to warn of the dangers of the product by failing to provide the FDA required "Medication Guide" consisting of language the FDA approved and required to go directly to the patient. The failure to provide the FDA "Mediation Guide" is a stronger claim than merely alleging the package insert or labeling fails to inform or warn patients or consumers of the dangers of the product The failure to provide each patient a "Medication Guide" by failing to provide the Medication Guides to the distributor for ultimate distribution to the patient with the drug is a direct violation of the FDA's mandate to the manufacturers of the drug intended to warn patients directly outside the communication with the prescribing physician, of the very dangers of amiodarone toxicity that injured Bobbye Jean Cooper.

COUNTS
COUNT 1 – NEGLIGENCE AND GROSS NEGLIGENCE

143. The paragraphs above are incorporated by reference hereto as if fully set forth at length.

144. Defendants owe a duty to design, test, manufacture, and market products for the uses for which they promote those products, including amiodarone, in such a way as to avoid harm to patient consumers, such as Bobbye Jean Cooper, and to refrain from such activities

following knowledge or constructive knowledge that the uses of its products are harming patient consumers who ingest them.

145. Defendants are each legally responsible in some manner for the wrongful events and occurrences alleged and each of them were in some manner legally responsible for causing Bobbye Jean Cooper's injuries and damages.

146. Defendants owed a duty to warn of the hazards and dangers associated with the off label uses of amiodarone that were never approved by FDA.

147. Defendants, acting by and through their authorized divisions, subsidiaries, agents, servants, and employees were guilty of carelessness, recklessness, negligence, gross negligence and willful, wanton, outrageous and reckless disregard for human life and safety in manufacturing, designing, labeling, marketing, distributing, supplying, selling, placing into the stream of commerce or some or all these actions amiodarone, both generally, and in the following particular respects:

a. failing to conduct adequate and appropriate testing of amiodarone;
b. failing to promptly and adequately warn of amiodarone's health risks;
c. failing to promptly, adequately, and appropriately recommend testing and monitoring of patients prescribed amiodarone, particularly for off label uses of amiodarone that were never approved by FDA;
d. failing to properly, appropriately, and adequately monitor amiodarone's post-market performance, particularly its performance when prescribed for off label uses of amiodarone that were never approved by FDA;
e. concealing from the FDA, National Institutes of Health, the general medical community, or medical professionals their full knowledge and experience regarding amiodarone's harm to humans, particularly when prescribed for off label uses were never approved by FDA;
f. promoting, marketing, advertising, selling or some or all of these actions for amiodarone use by patient consumers particularly when used off label for uses of amiodarone that were never approved by FDA, given Defendants knowledge and experience of amiodarone's potential harmful effects;
g. failing to take prompt and adequate measures to restrict off label uses of amiodarone that were never approved by FDA or warn of its potential dangers, given Defendants knowledge of amiodarone's potential harm to humans;

h. marketing off label uses of amiodarone that were never approved by FDA;
i. failing to disclose to medical professionals in an appropriate and timely manner, facts about amiodarone specifically related to off label uses of amiodarone that were never approved by FDA;
j. failing to exercise reasonable care to inform medical professionals about Defendants' own knowledge of amiodarone's potential harm to humans, particularly when used off label for uses of amiodarone that were never approved by FDA;
k. failing to provide consumer patients with the Medication Guide for amiodarone as required by FDA;

148. As a direct and proximate result of the negligent, reckless, wanton acts and omissions or some or all of this wrongful conduct by Defendants, Plaintiff and Bobbye Jean Cooper suffered damages, including injuries, pain and suffering, mental anguish, expenses, financial losses and other damages.

WHEREFORE, Bobbye Jean Cooper, requests that this Honorable Court enter judgment in her favor and against all Defendants jointly and severally in an amount in excess of $75,000.00, plus interest, costs, punitive damages, and attorney's fees.

COUNT II – STRICT LIABILITY

149. The paragraphs above are incorporated by reference hereto as if fully set forth at length.

150. As a result of the unreasonably dangerous and defective condition of amiodarone, particularly when used off label for uses that were never approved by FDA, that Defendants manufactured, designed, labeled, marketed, distributed, supplied, sold, placed into the stream of commerce or some or all of these activities, Bobbye Jean Cooper claims breach of strict liability by Defendants based on Defendants':

a. failing to properly and adequately design amiodarone, particularly when used off label for uses of amiodarone that were never approved by FDA;
b. failing to properly and adequately manufacture amiodarone, particularly when used off label for uses of amiodarone that were never approved by FDA; and,

c. improperly marketing amiodarone, particularly when marketing it off label for uses of amiodarone that were never approved by FDA.

151. The occurrences and injuries pled in this complaint were directly, proximately and producingly caused by Defendants' failures of design, manufacturing, and marketing as described in this complaint.

WHEREFORE, Bobbye Jean Cooper requests that this Honorable Court enter judgment in his favor and against Defendants jointly and severally, in an amount in excess of $75,000.00 plus interest, costs, punitive damages, and attorney's fees.

COUNT III – BREACH OF EXPRESS WARRANTY

152. The paragraphs above are incorporated by reference hereto as if set forth at length.

153. In marketing amiodarone, particularly when marketed off label for uses of amiodarone that were never approved by FDA, which was directed to consumer patients and medical professionals, Defendants warranted that amiodarone was both safe and effective marketed uses. Defendants so marketed amiodarone with the express intent to persuade them to use amiodarone, particularly for off label for uses that were never approved by FDA.

154. These warranties were breached by Defendants in that amiodarone was never approved for off label uses, never tested for off label uses, never proven safe or effective, and, as known to Defendants, constituted a serious danger to the safety of consumer patients.

155. As a direct, proximate and producing result of Defendants' breach of express warranty, Bobbye Jean Cooper suffered damages, including injuries, pain and suffering, mental anguish, expenses, financial losses and other damages.

WHEREFORE, Bobbye Jean Cooper requests that this Honorable Court enter judgment in her favor and against Defendants jointly and severally in an amount in excess of $75,000.00 plus interest, costs, punitive damages, and attorney's fees.

COUNT IV—FRAUD

156. The paragraphs above are incorporated by reference hereto as if set forth at length.

157. Defendants knowingly marketed amiodarone off label for uses of amiodarone that were never approved by FDA when they knew amiodarone was not approved for these uses, and had never been tested for the safety and efficacy of these uses. They misrepresented directly and indirectly that the marketed off label uses were safe and effective despite their knowledge that they were not. They knowingly concealed the risks of the marketed off label uses. They knowingly concealed their involvement in the misleading seminars and publications marketing the safety and efficacy of off label uses. They omitted information about amiodarone that evidenced the drug was neither safe nor effective for off label uses. They committed these acts and made these representations with the intent that consumer patients and medical professionals would rely on this incorrect and incomplete information and use amiodarone for off label for uses that were never approved by FDA. They committed these acts and made these representations for the intended purpose of increasing sales, revenue and profit at expense of patient safety. Defendants, therefore, are guilty of common law fraud that directly, proximately and producingly caused Bobbye Jean Cooper to suffer damages, including injuries, pain and suffering, mental anguish, expenses, financial losses and other damages.

WHEREFORE, Bobbye Jean Cooper requests that this Honorable Court enter judgment in her favor and against Defendants jointly and severally in an amount in excess of $75,000.00 plus interest, costs, punitive damages, and attorney's fees.

WHEREFORE**,** Bobbye Jean Cooper demands judgment against each Defendant jointly and severally for compensatory and punitive together with applicable interest, costs of suit, attorneys' fees and all such other relief as the Court deems proper.

V. DEMAND FOR JURY TRIAL

Plaintiff in the above-styled case hereby demands a trial by jury of all issues so triable as a matter of right.

This the 19th day of May, 2016

Respectfully Submitted,

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ATTORNEYS FOR PLAINTIFF
Bobbye Jean Cooper

EXHIBIT “A”

United States Code Annotated
Title 21. Food and Drugs (Refs & Annos)
Chapter 9. Federal Food, Drug, and Cosmetic Act (Refs & Annos)
Subchapter III. Prohibited Acts and Penalties

21 U.S.C.A. § 331

§ 331. Prohibited acts

Effective: December 28, 2015
Currentness

The following acts and the causing thereof are prohibited:

(a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded.

(b) The adulteration or misbranding of any food, drug, device, tobacco product, or cosmetic in interstate commerce.

(c) The receipt in interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.

(d) The introduction or delivery for introduction into interstate commerce of any article in violation of section 344, 350d, 355, or 360bbb-3 of this title.

(e) The refusal to permit access to or copying of any record as required by section 350a, 350c, 350f(j), 350e, 354, 360bbb-3, 373, 374(a), 379aa, or 379aa-1 of this title; or the failure to establish or maintain any record, or make any report, required under section 350a, 350c(b), 350f, 350e, 354, 355(i) or (k), 360b(a)(4)(C), 360b(j), (l) or (m), 360ccc-1(i), 360e(f), 360i, 360bbb-3, 379aa, 379aa-1, 387i, or 387t of this title or the refusal to permit access to or verification or copying of any such required record; or the violation of any recordkeeping requirement under section 2223 of this title (except when such violation is committed by a farm).

(f) The refusal to permit entry or inspection as authorized by section 374 of this title.

(g) The manufacture within any Territory of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded.

(h) The giving of a guaranty or undertaking referred to in section 333(c)(2) of this title, which guaranty or undertaking is false, except by a person who relied upon a guaranty or undertaking to the same effect signed by, and containing the name and address of, the person residing in the United States from whom he received in good faith the food, drug, device, tobacco product, or cosmetic; or the giving of a guaranty or undertaking referred to in section 333(c)(3) of this title, which guaranty or undertaking is false.

(i)(1) Forging, counterfeiting, simulating, or falsely representing, or without proper authority using any mark, stamp, tag, label, or other identification device authorized or required by regulations promulgated under the provisions of section 344 or 379e of this title.

(2) Making, selling, disposing of, or keeping in possession, control, or custody, or concealing any punch, die, plate, stone, or other thing designed to print, imprint, or reproduce the trademark, trade name, or other identifying mark, imprint, or device of another or any likeness of any of the foregoing upon any drug or container or labeling thereof so as to render such drug a counterfeit drug.

(3) The doing of any act which causes a drug to be a counterfeit drug, or the sale or dispensing, or the holding for sale or dispensing, of a counterfeit drug.

(j) The using by any person to his own advantage, or revealing, other than to the Secretary or officers or employees of the Department, or to the courts when relevant in any judicial proceeding under this chapter, any information acquired under authority of section 344, 348, 350a, 350c, 355, 360, 360b, 360c, 360d, 360e, 360f, 360h, 360i, 360j, 360ccc, 360ccc-1, 360ccc-2, 374, 379, 379e, 387d, 387e, 387f, 387g, 387h, 387i, or 387t(b) of this title concerning any method or process which as a trade secret is entitled to protection; or the violating of section 346a(i)(2) of this title or any regulation issued under that section.. [1] This paragraph does not authorize the withholding of information from either House of Congress or from, to the extent of matter within its jurisdiction, any committee or subcommittee of such committee or any joint committee of Congress or any subcommittee of such joint committee.

(k) The alteration, mutilation, destruction, obliteration, or removal of the whole or any part of the labeling of, or the doing of any other act with respect to, a food, drug, device, tobacco product, or cosmetic, if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded.

(l) Repealed. Pub.L. 105-115, Title IV, § 421, Nov. 21, 1997, 111 Stat. 2380.

(m) The sale or offering for sale of colored oleomargarine or colored margarine, or the possession or serving of colored oleomargarine or colored margarine in violation of subsections (b) or (c) of section 347 of this title.

(n) The using, in labeling, advertising or other sales promotion of any reference to any report or analysis furnished in compliance with section 374 of this title.

(o) In the case of a prescription drug distributed or offered for sale in interstate commerce, the failure of the manufacturer, packer, or distributor thereof to maintain for transmittal, or to transmit, to any practitioner licensed by applicable State law to administer such drug who makes written request for information as to such drug, true and correct copies of all printed matter which is required to be included in any package in which that drug is distributed or sold, or such other printed matter as is approved by the Secretary. Nothing in this paragraph shall be construed to exempt any person from any labeling requirement imposed by or under other provisions of this chapter.

(p) The failure to register in accordance with section 360 or 387e of this title, the failure to provide any information required by section 360(j), 360(k), 387e(i), or 387e(j) of this title, or the failure to provide a notice required by section 360(j)(2) or 387e(i)(3) of this title.

(q)(1) The failure or refusal

(A) to comply with any requirement prescribed under section 360h, 360j(g), 387c(b), 387g, 387h, or 387*o* of this title;

(B) to furnish any notification or other material or information required by or under section 360i, 360j(g), 387d, 387i, or 387t of this title; or

(C) to comply with a requirement under section 360*l* or 387m of this title.

(2) With respect to any device or tobacco product, the submission of any report that is required by or under this chapter that is false or misleading in any material respect.

(r) The movement of a device or tobacco product in violation of an order under section 334(g) of this title or the removal or alteration of any mark or label required by the order to identify the device or tobacco product as detained.

(s) The failure to provide the notice required by section 350a(c) or 350a(e) of this title, the failure to make the reports required by section 350a(f)(1)(B) of this title, the failure to retain the records required by section 350a(b)(4) of this title, or the failure to meet the requirements prescribed under section 350a(f)(3) of this title.

(t) The importation of a drug in violation of section 381(d)(1) of this title, the sale, purchase, or trade of a drug or drug sample or the offer to sell, purchase, or trade a drug or drug sample in violation of section 353(c) of this title, the sale, purchase, or trade of a coupon, the offer to sell, purchase, or trade such a coupon, or the counterfeiting of such a coupon in violation of section 353(c)(2) of this title, the distribution of a drug sample in violation of section 353(d) of this title or the failure to otherwise comply with the requirements of section 353(d) of this title, the distribution of drugs in violation of section 353(e) of this title, failure to comply with the requirements under section 360eee-1 of this title, the failure to comply with the requirements under section 360eee-3 of this title, as applicable, or the failure to otherwise comply with the requirements of section 353(e) of this title.

(u) The failure to comply with any requirements of the provisions of, or any regulations or orders of the Secretary, under section 360b(a)(4)(A), 360b(a)(4)(D), or 360b(a)(5) of this title.

(v) The introduction or delivery for introduction into interstate commerce of a dietary supplement that is unsafe under section 350b of this title.

(w) The making of a knowingly false statement in any statement, certificate of analysis, record, or report required or requested under section 381(d)(3) of this title; the failure to submit a certificate of analysis as required under such section; the failure to maintain records or to submit records or reports as required by such section; the release into interstate commerce of any

article or portion thereof imported into the United States under such section or any finished product made from such article or portion, except for export in accordance with section 381(e) or 382 of this title, or with section 262(h) of Title 42; or the failure to so export or to destroy such an article or portions thereof, or such a finished product.

(x) The falsification of a declaration of conformity submitted under section 360d(c) of this title or the failure or refusal to provide data or information requested by the Secretary under paragraph (3) of such section.

(y) In the case of a drug, device, or food--

(1) the submission of a report or recommendation by a person accredited under section 360m of this title that is false or misleading in any material respect;

(2) the disclosure by a person accredited under section 360m of this title of confidential commercial information or any trade secret without the express written consent of the person who submitted such information or secret to such person; or

(3) the receipt by a person accredited under section 360m of this title of a bribe in any form or the doing of any corrupt act by such person associated with a responsibility delegated to such person under this chapter.

(z) Omitted

(aa) The importation of a prescription drug in violation of section 384 of this title, the falsification of any record required to be maintained or provided to the Secretary under such section, or any other violation of regulations under such section.

(bb) The transfer of an article of food in violation of an order under section 334(h) of this title, or the removal or alteration of any mark or label required by the order to identify the article as detained.

(cc) The importing or offering for import into the United States of an article of food by, with the assistance of, or at the direction of, a person debarred under section 335a(b)(3) of this title.

(dd) The failure to register in accordance with section 350d of this title.

(ee) The importing or offering for import into the United States of an article of food in violation of the requirements under section 381(m) of this title.

(ff) The importing or offering for import into the United States of a drug or device with respect to which there is a failure to comply with a request of the Secretary to submit to the Secretary a statement under section 381(o) of this title.

(gg) The knowing failure to comply with paragraph (7)(E) of section 374(g) of this title; the knowing inclusion by a person accredited under paragraph (2) of such section of false information in an inspection report under paragraph (7)(A) of such section; or the knowing failure of such a person to include material facts in such a report.

(hh) The failure by a shipper, carrier by motor vehicle or rail vehicle, receiver, or any other person engaged in the transportation of food to comply with the sanitary transportation practices prescribed by the Secretary under section 350e of this title.

(ii) The falsification of a report of a serious adverse event submitted to a responsible person (as defined under section 379aa or 379aa-1 of this title) or the falsification of a serious adverse event report (as defined under section 379aa or 379aa-1 of this title) submitted to the Secretary.

(jj)(1) The failure to submit the certification required by section 282(j)(5)(B) of Title 42, or knowingly submitting a false certification under such section.

(2) The failure to submit clinical trial information required under subsection (j) of section 282 of Title 42.

(3) The submission of clinical trial information under subsection (j) of section 282 of Title 42 that is false or misleading in any particular under paragraph (5)(D) of such subsection (j).

(kk) The dissemination of a television advertisement without complying with section 353c of this title.

(ll) The introduction or delivery for introduction into interstate commerce of any food to which has been added a drug approved under section 355 of this title, a biological product licensed under section 262 of Title 42, or a drug or a biological product for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, unless--

(1) such drug or such biological product was marketed in food before any approval of the drug under section 355 of this title, before licensure of the biological product under such section 262 of Title 42, and before any substantial clinical investigations involving the drug or the biological product have been instituted;

(2) the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, approving the use of such drug or such biological product in the food;

(3) the use of the drug or the biological product in the food is to enhance the safety of the food to which the drug or the biological product is added or applied and not to have independent biological or therapeutic effects on humans, and the use is in conformity with--

(A) a regulation issued under section 348 of this title prescribing conditions of safe use in food;

(B) a regulation listing or affirming conditions under which the use of the drug or the biological product in food is generally recognized as safe;

(C) the conditions of use identified in a notification to the Secretary of a claim of exemption from the premarket approval requirements for food additives based on the notifier's determination that the use of the drug or the biological product in food is generally recognized as safe, provided that the Secretary has not questioned the general recognition of safety determination in a letter to the notifier;

(D) a food contact substance notification that is effective under section 348(h) of this title; or

(E) such drug or biological product had been marketed for smoking cessation prior to September 27, 2007; or

(4) the drug is a new animal drug whose use is not unsafe under section 360b of this title.

(mm) The failure to submit a report or provide a notification required under section 350f(d) of this title.

(nn) The falsification of a report or notification required under section 350f(d) of this title.

(oo) The sale of tobacco products in violation of a no-tobacco-sale order issued under section 333(f) of this title.

(pp) The introduction or delivery for introduction into interstate commerce of a tobacco product in violation of section 387k of this title.

(qq)(1) Forging, counterfeiting, simulating, or falsely representing, or without proper authority using any mark, stamp (including tax stamp), tag, label, or other identification device upon any tobacco product or container or labeling thereof so as to render such tobacco product a counterfeit tobacco product.

(2) Making, selling, disposing of, or keeping in possession, control, or custody, or concealing any punch, die, plate, stone, or other item that is designed to print, imprint, or reproduce the trademark, trade name, or other identifying mark, imprint, or device of another or any likeness of any of the foregoing upon any tobacco product or container or labeling thereof so as to render such tobacco product a counterfeit tobacco product.

(3) The doing of any act that causes a tobacco product to be a counterfeit tobacco product, or the sale or dispensing, or the holding for sale or dispensing, of a counterfeit tobacco product.

(rr) The charitable distribution of tobacco products.

(ss) The failure of a manufacturer or distributor to notify the Attorney General and the Secretary of the Treasury of their knowledge of tobacco products used in illicit trade.

(tt) Making any express or implied statement or representation directed to consumers with respect to a tobacco product, in a label or labeling or through the media or advertising, that either conveys, or misleads or would mislead consumers into believing, that

(1) the product is approved by the Food and Drug Administration;

(2) the Food and Drug Administration deems the product to be safe for use by consumers;

(3) the product is endorsed by the Food and Drug Administration for use by consumers; or

(4) the product is safe or less harmful by virtue of--

(A) its regulation or inspection by the Food and Drug Administration; or

(B) its compliance with regulatory requirements set by the Food and Drug Administration;

including any such statement or representation rendering the product misbranded under section 387c of this title.

(uu) The operation of a facility that manufactures, processes, packs, or holds food for sale in the United States if the owner, operator, or agent in charge of such facility is not in compliance with section 350g of this title.

(vv) The failure to comply with the requirements under section 350h of this title.

(ww) The failure to comply with section 350i of this title.

(xx) The refusal or failure to follow an order under section 350*l* of this title.

(yy) The knowing and willful failure to comply with the notification requirement under section 350f(h) of this title.

(zz) The importation or offering for importation of a food if the importer (as defined in section 384a of this title) does not have in place a foreign supplier verification program in compliance with such section 384a of this title.

(aaa) The failure to register in accordance with section 381(s) of this title.

(bbb) The failure to notify the Secretary in violation of section 360bbb-7 of this title.

(ccc)(1) The resale of a compounded drug that is labeled "not for resale" in accordance with section 353b of this title.

(2) With respect to a drug to be compounded pursuant to section 353a or 353b of this title, the intentional falsification of a prescription, as applicable.

(3) The failure to report drugs or adverse events by an entity that is registered in accordance with subsection (b) of section 353b of this title.

(ddd)(1) The manufacture or the introduction or delivery for introduction into interstate commerce of a rinse-off cosmetic that contains intentionally-added plastic microbeads.

(2) In this paragraph--

(A) the term "plastic microbead" means any solid plastic particle that is less than five millimeters in size and is intended to be used to exfoliate or cleanse the human body or any part thereof; and

(B) the term "rinse-off cosmetic" includes toothpaste.

CREDIT(S)

(June 25, 1938, c. 675, § 301, 52 Stat. 1042; 1940 Reorg. Plan No. IV, § 12, eff. June 30, 1940, 5 F.R. 2422, 54 Stat. 1237; Dec. 22, 1941, c. 613, § 1, 55 Stat. 851; July 6, 1945, c. 281, § 1, 59 Stat. 463; Mar. 10, 1947, c. 16, § 1, 61 Stat. 11; June 24, 1948, c. 613, § 1, 62 Stat. 582; Mar. 16, 1950, c. 61, § 3(b), 64 Stat. 20; 1953 Reorg. Plan No. 1, § 5, eff. Apr. 11, 1953, 18 F.R. 2053, 67 Stat. 631; Aug. 7, 1953, c. 350, § 2, 67 Stat. 477; Sept. 6, 1958, Pub.L. 85-929, § 5, 72 Stat. 1788; July 12, 1960, Pub.L. 86-618, Title I, §§ 104, 105(a), 74 Stat. 403; Oct. 10, 1962, Pub.L. 87-781, Title I, §§ 103(c), 104(e)(1), 106(c), 114(a), Title III, § 304, 76 Stat. 784, 785, 788, 791, 795; July 15, 1965, Pub.L. 89-74, §§ 5, 9(c), 79 Stat. 232, 235; July 13, 1968, Pub.L. 90-399, § 103, 82 Stat. 352; Oct. 24, 1968, Pub.L. 90-639, § 2(b), 82 Stat. 1361; Oct. 27, 1970, Pub.L. 91-513, Title II, § 701(a), 84 Stat. 1281; Aug. 16, 1972, Pub.L. 92-387, § 4(e), 86 Stat. 562; May 28, 1976, Pub.L. 94-295, §§ 3(b), 4(b)(1), 7(b), 90 Stat. 576, 580, 582; Sept. 26, 1980, Pub.L. 96-359, § 5, 94 Stat. 1193; Oct. 27, 1986, Pub.L. 99-570, Title IV, § 4014(b)(2), 100 Stat. 3207-120; Apr. 22, 1988, Pub.L. 100-293, § 7(a), 102 Stat. 99; Nov. 3, 1990, Pub.L. 101-502, § 5(j), 104 Stat. 1289; Nov. 5, 1990, Pub.L. 101-508, Title IV, § 4755(c)(2), 104 Stat. 1388-210; June 16, 1992, Pub.L. 102-300, § 3(a)(1), 106 Stat. 239; Oct. 29, 1992, Pub.L. 102-571, Title I, § 107(2), (3), 106 Stat. 4499; Aug. 13, 1993, Pub.L. 103-80, § 3(c), 107 Stat. 775; Oct. 22, 1994, Pub.L. 103-396, § 2(b)(1), 108 Stat. 4154; Oct. 25, 1994, Pub.L. 103-417, § 10(b), 108 Stat. 4332; Apr. 26, 1996, Pub.L. 104-134, Title II, § 2103, 110 Stat. 1321-319; Aug. 3, 1996, Pub.L. 104-170, Title IV, § 403, 110 Stat. 1514; Oct. 9, 1996, Pub.L. 104-250, § 5(d), 110 Stat. 3156; Nov. 21, 1997, Pub.L. 105-115, Title I, § 125(a)(2)(A), (C), (b)(2)(B), Title II, §§ 204(b), 210(c), Title IV, §§ 401(b), 421, 111 Stat. 2325, 2336, 2345, 2364, 2380; Oct. 28, 2000, Pub.L. 106-387, § 1(a) [Title VII, § 745(d)(1)], 114 Stat. 1549, 1549A-39; June 12, 2002, Pub.L. 107-188, Title III, §§ 303(b), 304(d), 305(b), 306(c), 307(b), 321(b)(2), 322(b), 116 Stat. 665, 666, 668, 670, 672, 676, 677; Oct. 26, 2002, Pub.L. 107-250, Title II, § 201(d), 116 Stat. 1609; Nov. 24, 2003, Pub.L. 108-136, Div. A, Title XVI, § 1603(c), 117 Stat. 1690; Dec. 8, 2003, Pub.L. 108-173, Title XI, § 1121(b)(1), 117 Stat. 2469; Apr. 1, 2004, Pub.L. 108-214, § 2(b)(2)(A), 118 Stat. 575; Aug. 2, 2004, Pub.L. 108-282, Title I, § 102(b)(5)(C), (D), 118 Stat. 902; Aug. 10, 2005, Pub.L. 109-59, Title VII, § 7202(d), (e), 119 Stat. 1913; Dec. 22, 2006, Pub.L. 109-462, §§ 2(c), 3(b), 4(a), 120 Stat. 3472, 3475; Sept. 27, 2007, Pub.L. 110-85, Title VIII, § 801(b)(1), Title IX, §§ 901(d)(1), 912(a), Title X, § 1005(d), 121 Stat. 920, 939, 951, 968; June 22, 2009, Pub.L. 111-31, Div. A, Title I, § 103(b), 123 Stat. 1833; Jan. 4, 2011, Pub.L. 111-353, Title I, §§ 102(d)(1), 103(e), 105(c), 106(d), Title II, §§ 204(j), 206(d), 211(b), (c), Title III, § 301(b), 124 Stat. 3889, 3898, 3904, 3906, 3937, 3943, 3953, 3954; Pub.L. 112-144, Title VII, §§ 714(a), 715(a), July 9, 2012, 126 Stat. 1073, 1075; Pub.L. 113-54, Title I, § 103(a), Title II, § 206(a), Nov. 27, 2013, 127 Stat. 597, 639; Pub.L. 114-114, § 2(a), Dec. 28, 2015, 129 Stat. 3129.)

Footnotes

1 So in original.

21 U.S.C.A. § 331, 21 USCA § 331

Current through P.L. 114-143. Also includes P.L. 114-145, 114-146, and 114-148.

End of Document

EXHIBIT “B”

21 U.S.C.A. § 352

§ 352. Misbranded drugs and devices

Effective: November 27, 2013
Currentness

A drug or device shall be deemed to be misbranded--

(a) False or misleading label

If its labeling is false or misleading in any particular. Health care economic information provided to a formulary committee, or other similar entity, in the course of the committee or the entity carrying out its responsibilities for the selection of drugs for managed care or other similar organizations, shall not be considered to be false or misleading under this paragraph if the health care economic information directly relates to an indication approved under section 355 of this title or under section 262(a) of Title 42 for such drug and is based on competent and reliable scientific evidence. The requirements set forth in section 355(a) of this title or in section 262(a) of Title 42 shall not apply to health care economic information provided to such a committee or entity in accordance with this paragraph. Information that is relevant to the substantiation of the health care economic information presented pursuant to this paragraph shall be made available to the Secretary upon request. In this paragraph, the term "health care economic information" means any analysis that identifies, measures, or compares the economic consequences, including the costs of the represented health outcomes, of the use of a drug to the use of another drug, to another health care intervention, or to no intervention.

(b) Package form; contents of label

If in package form unless it bears a label containing (1) the name and place of business of the manufacturer, packer, or distributor; and (2) an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count: *Provided*, That under clause (2) of this paragraph reasonable variations shall be permitted, and exemptions as to small packages shall be established, by regulations prescribed by the Secretary.

(c) Prominence of information on label

If any word, statement, or other information required by or under authority of this chapter to appear on the label or labeling is not prominently placed thereon with such conspicuousness (as compared with other words, statements, designs, or devices, in the labeling) and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use.

(d) Repealed. Pub.L. 105-115, Title I, § 126(b), Nov. 21, 1997, 111 Stat. 2327

(e) Designation of drugs or devices by established names

(1)(A) If it is a drug, unless its label bears, to the exclusion of any other nonproprietary name (except the applicable systematic chemical name or the chemical formula)--

(i) the established name (as defined in subparagraph (3)) of the drug, if there is such a name;

(ii) the established name and quantity or, if determined to be appropriate by the Secretary, the proportion of each active ingredient, including the quantity, kind, and proportion of any alcohol, and also including whether active or not the established name and quantity or if determined to be appropriate by the Secretary, the proportion of any bromides, ether, chloroform, acetanilide, acetophenetidin, amidopyrine, antipyrine, atropine, hyoscine, hyoscyamine, arsenic, digitalis, digitalis glucosides, mercury, ouabain, strophanthin, strychnine, thyroid, or any derivative or preparation of any such substances, contained therein, except that the requirement for stating the quantity of the active ingredients, other than the quantity of those specifically named in this subclause, shall not apply to nonprescription drugs not intended for human use; and

(iii) the established name of each inactive ingredient listed in alphabetical order on the outside container of the retail package and, if determined to be appropriate by the Secretary, on the immediate container, as prescribed in regulation promulgated by the Secretary, except that nothing in this subclause shall be deemed to require that any trade secret be divulged, and except that the requirements of this subclause with respect to alphabetical order shall apply only to nonprescription drugs that are not also cosmetics and that this subclause shall not apply to nonprescription drugs not intended for human use.

(B) For any prescription drug the established name of such drug or ingredient, as the case may be, on such label (and on any labeling on which a name for such drug or ingredient is used) shall be printed prominently and in type at least half as large as that used thereon for any proprietary name or designation for such drug or ingredient, except that to the extent that compliance with the requirements of subclause (ii) or (iii) of clause (A) or this clause is impracticable, exemptions shall be established by regulations promulgated by the Secretary.

(2) If it is a device and it has an established name, unless its label bears, to the exclusion of any other nonproprietary name, its established name (as defined in subparagraph (4)) prominently printed in type at least half as large as that used thereon for any proprietary name or designation for such device, except that to the extent compliance with the requirements of this subparagraph is impracticable, exemptions shall be established by regulations promulgated by the Secretary.

(3) As used in subparagraph (1), the term “established name”, with respect to a drug or ingredient thereof, means (A) the applicable official name designated pursuant to section 358 of this title, or (B), if there is no such name and such drug, or such ingredient, is an article recognized in an official compendium, then the official title thereof in such compendium, or (C) if neither clause (A) nor clause (B) of this subparagraph applies, then the common or usual name, if any, of such drug or of such ingredient, except that where clause (B) of this subparagraph applies to an article recognized in the United States Pharmacopeia and in the Homœopathic Pharmacopœia under different official titles, the official title used in the United States Pharmacopeia shall apply unless it is labeled and offered for sale as a homœopathic drug, in which case the official title used in the Homœopathic Pharmacopœia shall apply.

(4) As used in subparagraph (2), the term "established name" with respect to a device means (A) the applicable official name of the device designated pursuant to section 358 of this title, (B) if there is no such name and such device is an article recognized in an official compendium, then the official title thereof in such compendium, or (C) if neither clause (A) nor clause (B) of this subparagraph applies, then any common or usual name of such device.

(f) Directions for use and warnings on label

Unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users, except that where any requirement of clause (1) of this paragraph, as applied to any drug or device, is not necessary for the protection of the public health, the Secretary shall promulgate regulations exempting such drug or device from such requirement. Required labeling for prescription devices intended for use in health care facilities or by a health care professional and required labeling for in vitro diagnostic devices intended for use by health care professionals or in blood establishments may be made available solely by electronic means, provided that the labeling complies with all applicable requirements of law, and that the manufacturer affords such users the opportunity to request the labeling in paper form, and after such request, promptly provides the requested information without additional cost.

(g) Representations as recognized drug; packing and labeling; inconsistent requirements for designation of drug

If it purports to be a drug the name of which is recognized in an official compendium, unless it is packaged and labeled as prescribed therein. The method of packing may be modified with the consent of the Secretary. Whenever a drug is recognized in both the United States Pharmacopœia and the Homœopathic Pharmacopœia of the United States, it shall be subject to the requirements of the United States Pharmacopœia with respect to packaging and labeling unless it is labeled and offered for sale as a homœopathic drug, in which case it shall be subject to the provisions of the Homœopathic Pharmacopœia of the United States, and not those of the United States Pharmacopœia, except that in the event of inconsistency between the requirements of this paragraph and those of paragraph (e) as to the name by which the drug or its ingredients shall be designated, the requirements of paragraph (e) shall prevail.

(h) Deteriorative drugs; packing and labeling

If it has been found by the Secretary to be a drug liable to deterioration, unless it is packaged in such form and manner, and its label bears a statement of such precautions, as the Secretary shall by regulations require as necessary for the protection of the public health. No such regulation shall be established for any drug recognized in an official compendium until the Secretary shall have informed the appropriate body charged with the revision of such compendium of the need for such packaging or labeling requirements and such body shall have failed within a reasonable time to prescribe such requirements.

(i) Drug; misleading container; imitation; offer for sale under another name

(1) If it is a drug and its container is so made, formed, or filled as to be misleading; or (2) if it is an imitation of another drug; or (3) if it is offered for sale under the name of another drug.

(j) Health-endangering when used as prescribed

If it is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof.

(k) Repealed. Pub.L. 105-115, Title I, § 125(a)(2)(B), Nov. 21, 1997, 111 Stat. 2325

(l) Repealed. Pub.L. 105-115, Title I, § 125(b)(2)(D), Nov. 21, 1997, 111 Stat. 2325

(m) Color additives; packing and labeling

If it is a color additive the intended use of which is for the purpose of coloring only, unless its packaging and labeling are in conformity with such packaging and labeling requirements applicable to such color additive, as may be contained in regulations issued under section 379e of this title.

(n) Prescription drug advertisements: established name; quantitative formula; side effects, contraindications, and effectiveness; prior approval; false advertising; labeling; construction of the Convention on Psychotropic Substances

In the case of any prescription drug distributed or offered for sale in any State, unless the manufacturer, packer, or distributor thereof includes in all advertisements and other descriptive printed matter issued or caused to be issued by the manufacturer, packer, or distributor with respect to that drug a true statement of (1) the established name as defined in paragraph (e) of this section, printed prominently and in type at least half as large as that used for any trade or brand name thereof, (2) the formula showing quantitatively each ingredient of such drug to the extent required for labels under paragraph (e) of this section, and (3) such other information in brief summary relating to side effects, contraindications, and effectiveness as shall be required in regulations which shall be issued by the Secretary in accordance with section 371(a) of this title, and in the case of published direct-to-consumer advertisements the following statement printed in conspicuous text: “You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.”, except that (A) except in extraordinary circumstances, no regulation issued under this paragraph shall require prior approval by the Secretary of the content of any advertisement, and (B) no advertisement of a prescription drug, published after the effective date of regulations issued under this paragraph applicable to advertisements of prescription drugs, shall with respect to the matters specified in this paragraph or covered by such regulations, be subject to the provisions of sections 52 to 57 of Title 15. This paragraph (n) shall not be applicable to any printed matter which the Secretary determines to be labeling as defined in section 321(m) of this title. Nothing in the Convention on Psychotropic Substances, signed at Vienna, Austria, on February 21, 1971, shall be construed to prevent drug price communications to consumers. In the case of an advertisement for a drug subject to section 353(b)(1) of this title presented directly to consumers in television or radio format and stating the name of the drug and its conditions of use, the major statement relating to side effects and contraindications shall be presented in a clear, conspicuous, and neutral manner.

(o) Drugs or devices from nonregistered establishments

If it was manufactured, prepared, propagated, compounded, or processed in an establishment not duly registered under section 360 of this title, if it is a drug and was imported or offered for import by a commercial importer of drugs not duly registered under section 381(s) of this title, if it was not included in a list required by section 360(j) of this title, if a notice or other information respecting it was not provided as required by such section or section 360(k) of this title, or if it does not bear such symbols from the uniform system for identification of devices prescribed under section 360(e) of this title as the Secretary by regulation requires.

(p) Packaging or labeling of drugs in violation of regulations

If it is a drug and its packaging or labeling is in violation of an applicable regulation issued pursuant to section 1472 or 1473 of Title 15.

(q) Restricted devices using false or misleading advertising or used in violation of regulations

In the case of any restricted device distributed or offered for sale in any State, if (1) its advertising is false or misleading in any particular, or (2) it is sold, distributed, or used in violation of regulations prescribed under section 360j(e) of this title.

(r) Restricted devices not carrying requisite accompanying statements in advertisements and other descriptive printed matter

In the case of any restricted device distributed or offered for sale in any State, unless the manufacturer, packer, or distributor thereof includes in all advertisements and other descriptive printed matter issued or caused to be issued by the manufacturer, packer, or distributor with respect to that device (1) a true statement of the device's established name as defined in subsection (e) of this section, printed prominently and in type at least half as large as that used for any trade or brand name thereof, and (2) a brief statement of the intended uses of the device and relevant warnings, precautions, side effects, and contraindications and, in the case of specific devices made subject to a finding by the Secretary after notice and opportunity for comment that such action is necessary to protect the public health, a full description of the components of such device or the formula showing quantitatively each ingredient of such device to the extent required in regulations which shall be issued by the Secretary after an opportunity for a hearing. Except in extraordinary circumstances, no regulation issued under this paragraph shall require prior approval by the Secretary of the content of any advertisement and no advertisement of a restricted device, published after the effective date of this paragraph shall, with respect to the matters specified in this paragraph or covered by regulations issued hereunder, be subject to the provisions of sections 52 through 55 of Title 15. This paragraph shall not be applicable to any printed matter which the Secretary determines to be labeling as defined in section 321(m) of this title.

(s) Devices subject to performance standards not bearing requisite labeling

If it is a device subject to a performance standard established under section 360d of this title, unless it bears such labeling as may be prescribed in such performance standard.

(t) Devices for which there has been a failure or refusal to give required notification or to furnish required material or information

If it is a device and there was a failure or refusal (1) to comply with any requirement prescribed under section 360h of this title respecting the device, (2) to furnish any material or information required by or under section 360i of this title respecting the device, or (3) to comply with a requirement under section 360*l* of this title.

(u) Identification of manufacturer

(1) Subject to paragraph (2), if it is a reprocessed single-use device, unless it, or an attachment thereto, prominently and conspicuously bears the name of the manufacturer of the reprocessed device, a generally recognized abbreviation of such name, or a unique and generally recognized symbol identifying such manufacturer.

(2) If the original device or an attachment thereto does not prominently and conspicuously bear the name of the manufacturer of the original device, a generally recognized abbreviation of such name, or a unique and generally recognized symbol identifying such manufacturer, a reprocessed device may satisfy the requirements of paragraph (1) through the use of a detachable label on the packaging that identifies the manufacturer and is intended to be affixed to the medical record of a patient.

(v) Reprocessed single-use devices

If it is a reprocessed single-use device, unless all labeling of the device prominently and conspicuously bears the statement "Reprocessed device for single use. Reprocessed by ___." The name of the manufacturer of the reprocessed device shall be placed in the space identifying the person responsible for reprocessing.

(w) New animal drugs

If it is a new animal drug--

(1) that is conditionally approved under section 360ccc of this title and its labeling does not conform with the approved application or section 360ccc(f) of this title, or that is not conditionally approved under section 360ccc of this title and its label bears the statement set forth in section 360ccc(f)(1)(A) of this title; or

(2) that is indexed under section 360ccc-1 of this title and its labeling does not conform with the index listing under section 360ccc-1(e) of this title or 360ccc-1(h) of this title, or that has not been indexed under section 360ccc-1 of this title and its label bears the statement set forth in section 360ccc-1(h) of this title.

(x) Nonprescription drugs

If it is a nonprescription drug (as defined in section 379aa of this title) that is marketed in the United States, unless the label of such drug includes a domestic address or domestic phone number through which the responsible person (as described in section 379aa of this title) may receive a report of a serious adverse event (as defined in section 379aa of this title) with such drug.

(y) Drugs subject to approved risk evaluation and mitigation strategy

If it is a drug subject to an approved risk evaluation and mitigation strategy pursuant to section 355(p) of this title and the responsible person (as such term is used in section 355-1 of this title) fails to comply with a requirement of such strategy provided for under subsection (d), (e), or (f) of section 355-1 of this title.

(z) Postmarket studies and clinical trials; new safety information in labeling

If it is a drug, and the responsible person (as such term is used in section 355(o) of this title) is in violation of a requirement established under paragraph (3) (relating to postmarket studies and clinical trials) or paragraph (4) (relating to labeling) of section 355(o) of this title with respect to such drug.

(aa) Unpaid fees; failure to submit identifying information

If it is a drug, or an active pharmaceutical ingredient, and it was manufactured, prepared, propagated, compounded, or processed in a facility for which fees have not been paid as required by section 379j-42(a)(4) of this title or for which identifying information required by section 379j-42(f) of this title has not been submitted, or it contains an active pharmaceutical ingredient that was manufactured, prepared, propagated, compounded, or processed in such a facility.

(bb) If the advertising or promotion of a compounded drug is false or misleading in any particular.

(cc) If it is a drug and it fails to bear the product identifier as required by section 360eee-1 of this title.

CREDIT(S)

(June 25, 1938, c. 675, § 502, 52 Stat. 1050; June 23, 1939, c. 242, § 3, 53 Stat. 854; 1940 Reorg. Plan No. IV, §§ 12, 13, eff. June 30, 1940, 5 F.R. 2422, 54 Stat. 1237; Dec. 22, 1941, c. 613, § 2, 55 Stat. 851; July 6, 1945, c. 281, § 2, 59 Stat. 463; Mar. 10, 1947, c. 16, § 2, 61 Stat. 11; July 13, 1949, c. 305, § 1, 63 Stat. 409; 1953 Reorg. Plan No. 1, § 5, eff. Apr. 11, 1953, 18 F.R. 2053, 67 Stat. 631; Aug. 5, 1953, c. 334, § 1, 67 Stat. 389; July 12, 1960, Pub.L. 86-618, Title I, § 102(b)(2), 74 Stat. 398; Oct. 10, 1962, Pub.L. 87-781, Title I, §§ 105(c), 112(a), (b), 131(a), Title III, § 305, 76 Stat. 785, 790, 791, 795; July 13, 1968, Pub.L. 90-399, § 105(a), 82 Stat. 352; Dec. 30, 1970, Pub.L. 91-601, § 7(d), 84 Stat. 1673; Dec. 30, 1970, Pub.L. 91-601, § 6(d), formerly § 7(d), 84 Stat. 1673; renumbered § 6(d), Aug. 13, 1981, Pub.L. 97-35, Title XII, § 1205(c), 95 Stat. 716; amended May 28, 1976, Pub.L. 94-295, §§ 3(e), 4(b)(2), 5(a), 9(b)(2), 90 Stat. 577, 580, 583; Nov. 10, 1978, Pub.L. 95-633, Title I, § 111, 92 Stat. 3773; June 16, 1992, Pub.L. 102-300, § 3(a)(2), 106 Stat. 239; Oct. 29, 1992, Pub.L. 102-571, Title I, § 107(9), 106 Stat. 4499; Aug. 13, 1993, Pub.L. 103-80, § 3(m), 107 Stat. 777; Nov. 21, 1997, Pub.L. 105-115, Title I, §§ 114(a), 125(a)(2)(B), (b)(2)(D), 126(b), Title IV, § 412(c), 111 Stat. 2312, 2325, 2327, 2375; Oct. 26, 2002, Pub.L. 107-250, Title II, § 206, Title III, §§ 301(a), 302(a)(1), 116 Stat. 1613, 1616; Apr. 1, 2004, Pub.L. 108-214, § 2(b)(2)(B), (c)(1), 118 Stat. 575; Aug. 2, 2004, Pub.L. 108-282, Title I, § 102(b)(5)(E), 118 Stat. 902; Aug. 1, 2005, Pub.L. 109-43, § 2(c)(1), 119 Stat. 441; Dec. 22, 2006, Pub.L. 109-462, § 2(d), 120 Stat. 3472; Sept. 27, 2007, Pub.L. 110-85, Title IX, §§ 901(d)(3)(A), (6), 902(a), 906(a), 121 Stat. 940, 942, 943, 949; Pub.L. 112-144, Title III, § 306, Title VII, §§ 702(a), 714(c), July 9, 2012, 126 Stat. 1024, 1065, 1074; Pub.L. 112-193, § 2(a), Oct. 5, 2012, 126 Stat. 1443; Pub.L. 113-54, Title I, § 103(b), Title II, § 206(b), Nov. 27, 2013, 127 Stat. 597, 639.)

21 U.S.C.A. § 352, 21 USCA § 352
Current through P.L. 114-143. Also includes P.L. 114-145, 114-146, and 114-148.

End of Document

EXHIBIT “C”

United States Code Annotated
Title 21. Food and Drugs (Refs & Annos)
Chapter 9. Federal Food, Drug, and Cosmetic Act (Refs & Annos)
Subchapter V. Drugs and Devices
Part A. Drugs and Devices (Refs & Annos)

21 U.S.C.A. § 355

§ 355. New drugs

Effective: November 25, 2015
Currentness

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.

(b) Filing application; contents

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug, and (G) any assessments required under section 355c of this title. The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences. The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by clause (A).

(2) An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted shall also include--

(A) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking

approval under this subsection and for which information is required to be filed under paragraph (1) or subsection (c) of this section--

(i) that such patent information has not been filed,

(ii) that such patent has expired,

(iii) of the date on which such patent will expire, or

(iv) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(B) if with respect to the drug for which investigations described in paragraph (1)(A) were conducted information was filed under paragraph (1) or subsection (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

(3) Notice of opinion that patent is invalid or will not be infringed

(A) Agreement to give notice

An applicant that makes a certification described in paragraph (2)(A)(iv) shall include in the application a statement that the applicant will give notice as required by this paragraph.

(B) Timing of notice

An applicant that makes a certification described in paragraph (2)(A)(iv) shall give notice as required under this paragraph--

(i) if the certification is in the application, not later than 20 days after the date of the postmark on the notice with which the Secretary informs the applicant that the application has been filed; or

(ii) if the certification is in an amendment or supplement to the application, at the time at which the applicant submits the amendment or supplement, regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.

(C) Recipients of notice

An applicant required under this paragraph to give notice shall give notice to--

(i) each owner of the patent that is the subject of the certification (or a representative of the owner designated to receive such a notice); and

(ii) the holder of the approved application under this subsection for the drug that is claimed by the patent or a use of which is claimed by the patent (or a representative of the holder designated to receive such a notice).

(D) Contents of notice

A notice required under this paragraph shall--

(i) state that an application that contains data from bioavailability or bioequivalence studies has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification; and

(ii) include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed.

(4)(A) An applicant may not amend or supplement an application referred to in paragraph (2) to seek approval of a drug that is a different drug than the drug identified in the application as submitted to the Secretary.

(B) With respect to the drug for which such an application is submitted, nothing in this subsection or subsection (c)(3) of this section prohibits an applicant from amending or supplementing the application to seek approval of a different strength.

(5)(A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1) or under section 262 of Title 42, which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.

(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection or section 262 of Title 42 if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size--

(i)(I) of clinical trials intended to form the primary basis of an effectiveness claim; or

(II) in the case where human efficacy studies are not ethical or feasible, of animal and any associated clinical trials which, in combination, are intended to form the primary basis of an effectiveness claim; or

(ii) with respect to an application for approval of a biological product under section 262(k) of Title 42, of any necessary clinical study or studies.

The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of the clinical trials. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant upon request.

(C) Any agreement regarding the parameters of the design and size of clinical trials of a new drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except--

(i) with the written agreement of the sponsor or applicant; or

(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance division personnel unless such field or compliance division personnel demonstrate to the reviewing division why such decision should be modified.

(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.

(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection or section 262 of Title 42 (including all scientific and medical matters, chemistry, manufacturing, and controls).

(6) An application submitted under this subsection shall be accompanied by the certification required under section 282(j)(5)(B) of Title 42. Such certification shall not be considered an element of such application.

(c) Period for approval of application; period for, notice, and expedition of hearing; period for issuance of order

(1) Within one hundred and eighty days after the filing of an application under subsection (b) of this section, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either--

(A) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) of this section applies, or

(B) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) of this section on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on

an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(2) If the patent information described in subsection (b) of this section could not be filed with the submission of an application under subsection (b) of this section because the application was filed before the patent information was required under subsection (b) of this section or a patent was issued after the application was approved under such subsection, the holder of an approved application shall file with the Secretary the patent number and the expiration date of any patent which claims the drug for which the application was submitted or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If the holder of an approved application could not file patent information under subsection (b) of this section because it was not required at the time the application was approved, the holder shall file such information under this subsection not later than thirty days after September 24, 1984, and if the holder of an approved application could not file patent information under subsection (b) of this section because no patent had been issued when an application was filed or approved, the holder shall file such information under this subsection not later than thirty days after the date the patent involved is issued. Upon the submission of patent information under this subsection, the Secretary shall publish it.

(3) The approval of an application filed under subsection (b) of this section which contains a certification required by paragraph (2) of such subsection shall be made effective on the last applicable date determined by applying the following to each certification made under subsection (b)(2)(A) of this section:

(A) If the applicant only made a certification described in clause (i) or (ii) of subsection (b)(2)(A) of this section or in both such clauses, the approval may be made effective immediately.

(B) If the applicant made a certification described in clause (iii) of subsection (b)(2)(A) of this section, the approval may be made effective on the date certified under clause (iii).

(C) If the applicant made a certification described in clause (iv) of subsection (b)(2)(A) of this section, the approval shall be made effective immediately unless, before the expiration of 45 days after the date on which the notice described in subsection (b)(3) of this section is received, an action is brought for infringement of the patent that is the subject of the certification and for which information was submitted to the Secretary under paragraph (2) or subsection (b)(1) of this section before the date on which the application (excluding an amendment or supplement to the application) was submitted. If such an action is brought before the expiration of such days, the approval may be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under subsection (b)(3) of this section or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that--

(i) if before the expiration of such period the district court decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the approval shall be made effective on--

(I) the date on which the court enters judgment reflecting the decision; or

(II) the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed;

(ii) if before the expiration of such period the district court decides that the patent has been infringed--

(I) if the judgment of the district court is appealed, the approval shall be made effective on--

(aa) the date on which the court of appeals decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity); or

(bb) the date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid or not infringed; or

(II) if the judgment of the district court is not appealed or is affirmed, the approval shall be made effective on the date specified by the district court in a court order under section 271(e)(4)(A) of Title 35;

(iii) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not infringed, the approval shall be made effective as provided in clause (i); or

(iv) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent has been infringed, the approval shall be made effective as provided in clause (ii).

In such an action, each of the parties shall reasonably cooperate in expediting the action.

(D) Civil action to obtain patent certainty

(i) Declaratory judgment absent infringement action

(I) In general

No action may be brought under section 2201 of Title 28, by an applicant referred to in subsection (b)(2) of this section for a declaratory judgment with respect to a patent which is the subject of the certification referred to in subparagraph (C) unless--

(aa) the 45-day period referred to in such subparagraph has expired;

(bb) neither the owner of such patent nor the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brought a civil action against the applicant for infringement of the patent before the expiration of such period; and

(cc) in any case in which the notice provided under paragraph (2)(B) relates to noninfringement, the notice was accompanied by a document described in subclause (III).

(II) Filing of civil action

If the conditions described in items (aa), (bb), and as applicable, (cc) of subclause (I) have been met, the applicant referred to in such subclause may, in accordance with section 2201 of Title 28, bring a civil action under such section against the owner or holder referred to in such subclause (but not against any owner or holder that has brought such a civil action against the applicant, unless that civil action was dismissed without prejudice) for a declaratory judgment that the patent is invalid or will not be infringed by the drug for which the applicant seeks approval, except that such civil action may be brought for a declaratory judgment that the patent will not be infringed only in a case in which the condition described in subclause (I)(cc) is applicable. A civil action referred to in this subclause shall be brought in the judicial district where the defendant has its principal place of business or a regular and established place of business.

(III) Offer of confidential access to application

For purposes of subclause (I)(cc), the document described in this subclause is a document providing an offer of confidential access to the application that is in the custody of the applicant referred to in subsection (b)(2) of this section for the purpose of determining whether an action referred to in subparagraph (C) should be brought. The document providing the offer of confidential access shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract. Any person provided an offer of confidential access shall review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under subsection (b)(2)(A)(iv) of this section and for no other purpose, and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the applicant to remove any information of no relevance to any issue of patent infringement.

(ii) Counterclaim to infringement action

(I) In general

If an owner of the patent or the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) of this section or this subsection on the ground that the patent does not claim either--

(aa) the drug for which the application was approved; or

(bb) an approved method of using the drug.

(II) No independent cause of action

Subclause (I) does not authorize the assertion of a claim described in subclause (I) in any civil action or proceeding other than a counterclaim described in subclause (I).

(iii) No damages

An applicant shall not be entitled to damages in a civil action under clause (i) or a counterclaim under clause (ii).

(E)(i) If an application (other than an abbreviated new drug application) submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of another application for a drug for which the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted effective before the expiration of ten years from the date of the approval of the application previously approved under subsection (b) of this section.

(ii) If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application which refers to the drug for which the subsection (b) application was submitted and for which the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted may be submitted under subsection (b) of this section before the expiration of five years from the date of the approval of the application under subsection (b) of this section, except that such an application may be submitted under subsection (b) of this section after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in clause (iv) of subsection (b)(2)(A) of this section. The approval of such an application shall be made effective in accordance with this paragraph except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (C) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

(iii) If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) of this section for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the

date of the approval of the application under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

(iv) If a supplement to an application approved under subsection (b) of this section is approved after September 24, 1984, and the supplement contains reports of new clinical investigations (other than bioavailabilty [1] studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under subsection (b) of this section for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

(v) If an application (or supplement to an application) submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection and for which the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted and which refers to the drug for which the subsection (b) application was submitted effective before the expiration of two years from September 24, 1984.

(4) A drug manufactured in a pilot or other small facility may be used to demonstrate the safety and effectiveness of the drug and to obtain approval for the drug prior to manufacture of the drug in a larger facility, unless the Secretary makes a determination that a full scale production facility is necessary to ensure the safety or effectiveness of the drug.

(d) Grounds for refusing application; approval of application; "substantial evidence" defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) the application failed to contain the patent information prescribed by subsection (b) of this section; or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified

by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence. The Secretary shall implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decisionmaking, and the communication of the benefits and risks of new drugs. Nothing in the preceding sentence shall alter the criteria for evaluating an application for premarket approval of a drug.

(e) Withdrawal of approval; grounds; immediate suspension upon finding imminent hazard to public health

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) the patent information prescribed by subsection (c) of this section was not filed within thirty days after the receipt of written notice from the Secretary specifying the failure to file such information; or (5) that the application contains any untrue statement of a material fact: *Provided*, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application submitted under subsection (b) or (j) of this section with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (k) of this section or to comply with the notice requirements of section 360(k)(2) of this title, or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based. The Secretary may withdraw the approval of an application submitted under this section, or suspend the approval of such an application, as provided under this subsection, without first ordering the applicant to submit an assessment of the approved risk evaluation and mitigation strategy for the drug under section 355-1(g)(2)(D) of this title.

(f) Revocation of order refusing, withdrawing or suspending approval of application

Whenever the Secretary finds that the facts so require, he shall revoke any previous order under subsection (d) or (e) of this section refusing, withdrawing, or suspending approval of an application and shall approve such application or reinstate such approval, as may be appropriate.

(g) Service of orders

Orders of the Secretary issued under this section shall be served (1) in person by any officer or employee of the department designated by the Secretary or (2) by mailing the order by registered mail or by certified mail addressed to the applicant or respondent at his last-known address in the records of the Secretary.

(h) Appeal from order

An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of Title 28. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of Title 28. The commencement of proceedings under this subsection shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

(i) Exemptions of drugs for research; discretionary and mandatory conditions; direct reports to Secretary

(1) The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of the public health, provide for conditioning such exemption upon--

(A) the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, of preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing;

(B) the manufacturer or the sponsor of the investigation of a new drug proposed to be distributed to investigators for clinical testing obtaining a signed agreement from each of such investigators that patients to whom the drug is administered will be under his personal supervision, or under the supervision of investigators responsible to him, and that he will not supply such drug to any other investigator, or to clinics, for administration to human beings;

(C) the establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application pursuant to subsection (b) of this section; and

(D) the submission to the Secretary by the manufacturer or the sponsor of the investigation of a new drug of a statement of intent regarding whether the manufacturer or sponsor has plans for assessing pediatric safety and efficacy.

(2) Subject to paragraph (3), a clinical investigation of a new drug may begin 30 days after the Secretary has received from the manufacturer or sponsor of the investigation a submission containing such information about the drug and the clinical investigation, including--

(A) information on design of the investigation and adequate reports of basic information, certified by the applicant to be accurate reports, necessary to assess the safety of the drug for use in clinical investigation; and

(B) adequate information on the chemistry and manufacturing of the drug, controls available for the drug, and primary data tabulations from animal or human studies.

(3)(A) At any time, the Secretary may prohibit the sponsor of an investigation from conducting the investigation (referred to in this paragraph as a "clinical hold") if the Secretary makes a determination described in subparagraph (B). The Secretary shall specify the basis for the clinical hold, including the specific information available to the Secretary which served as the basis for such clinical hold, and confirm such determination in writing.

(B) For purposes of subparagraph (A), a determination described in this subparagraph with respect to a clinical hold is that--

(i) the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation, taking into account the qualifications of the clinical investigators, information about the drug, the design of the clinical investigation, the condition for which the drug is to be investigated, and the health status of the subjects involved; or

(ii) the clinical hold should be issued for such other reasons as the Secretary may by regulation establish (including reasons established by regulation before November 21, 1997).

(C) Any written request to the Secretary from the sponsor of an investigation that a clinical hold be removed shall receive a decision, in writing and specifying the reasons therefor, within 30 days after receipt of such request. Any such request shall include sufficient information to support the removal of such clinical hold.

(4) Regulations under paragraph (1) shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational purposes certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where it is not feasible or it is contrary to the best interests of such human beings. Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs. The Secretary shall update such regulations to require inclusion in the informed consent documents and process a statement that clinical trial information for such clinical investigation has been or will be submitted for inclusion in the registry data bank pursuant to subsection (j) of section 282 of Title 42.

(j) Abbreviated new drug applications

(1) Any person may file with the Secretary an abbreviated application for the approval of a new drug.

(2)(A) An abbreviated application for a new drug shall contain--

(i) information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a drug listed under paragraph (7) (hereinafter in this subsection referred to as a "listed drug");

(ii)(I) if the listed drug referred to in clause (i) has only one active ingredient, information to show that the active ingredient of the new drug is the same as that of the listed drug;

(II) if the listed drug referred to in clause (i) has more than one active ingredient, information to show that the active ingredients of the new drug are the same as those of the listed drug, or

(III) if the listed drug referred to in clause (i) has more than one active ingredient and if one of the active ingredients of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the other active ingredients of the new drug are the same as the active ingredients of the listed drug, information to show that the different active ingredient is an active ingredient of a listed drug or of a drug which does not meet the requirements of section 321(p) of this title, and such other information respecting the different active ingredient with respect to which the petition was filed as the Secretary may require;

(iii) information to show that the route of administration, the dosage form, and the strength of the new drug are the same as those of the listed drug referred to in clause (i) or, if the route of administration, the dosage form, or the strength of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), such information respecting the route of administration, dosage form, or strength with respect to which the petition was filed as the Secretary may require;

(iv) information to show that the new drug is bioequivalent to the listed drug referred to in clause (i), except that if the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug referred to in

clause (i) and the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in clause (i);

(v) information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug referred to in clause (i) except for changes required because of differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers;

(vi) the items specified in clauses (B) through (F) of subsection (b)(1) of this section;

(vii) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the listed drug referred to in clause (i) or which claims a use for such listed drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under subsection (b) or (c) of this section--

(I) that such patent information has not been filed,

(II) that such patent has expired,

(III) of the date on which such patent will expire, or

(IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(viii) if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii).

(B) Notice of opinion that patent is invalid or will not be infringed

(i) Agreement to give notice

An applicant that makes a certification described in subparagraph (A)(vii)(IV) shall include in the application a statement that the applicant will give notice as required by this subparagraph.

(ii) Timing of notice

An applicant that makes a certification described in subparagraph (A)(vii)(IV) shall give notice as required under this subparagraph--

(I) if the certification is in the application, not later than 20 days after the date of the postmark on the notice with which the Secretary informs the applicant that the application has been filed; or

(II) if the certification is in an amendment or supplement to the application, at the time at which the applicant submits the amendment or supplement, regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.

(iii) Recipients of notice

An applicant required under this subparagraph to give notice shall give notice to--

(I) each owner of the patent that is the subject of the certification (or a representative of the owner designated to receive such a notice); and

(II) the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent (or a representative of the holder designated to receive such a notice).

(iv) Contents of notice

A notice required under this subparagraph shall--

(I) state that an application that contains data from bioavailability or bioequivalence studies has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification; and

(II) include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed.

(C) If a person wants to submit an abbreviated application for a new drug which has a different active ingredient or whose route of administration, dosage form, or strength differ from that of a listed drug, such person shall submit a petition to the Secretary seeking permission to file such an application. The Secretary shall approve or disapprove a petition submitted under this subparagraph within ninety days of the date the petition is submitted. The Secretary shall approve such a petition unless the Secretary finds--

(i) that investigations must be conducted to show the safety and effectiveness of the drug or of any of its active ingredients, the route of administration, the dosage form, or strength which differ from the listed drug; or

(ii) that any drug with a different active ingredient may not be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted in an abbreviated application.

(D)(i) An applicant may not amend or supplement an application to seek approval of a drug referring to a different listed drug from the listed drug identified in the application as submitted to the Secretary.

(ii) With respect to the drug for which an application is submitted, nothing in this subsection prohibits an applicant from amending or supplementing the application to seek approval of a different strength.

(iii) Within 60 days after December 8, 2003, the Secretary shall issue guidance defining the term "listed drug" for purposes of this subparagraph.

(3)(A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1), which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.

(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of bioavailability and bioequivalence studies needed for approval of such application. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of such studies. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant.

(C) Any agreement regarding the parameters of design and size of bioavailability and bioequivalence studies of a drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except--

(i) with the written agreement of the sponsor or applicant; or

(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance office personnel unless such field or compliance office personnel demonstrate to the reviewing division why such decision should be modified.

(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.

(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection (including scientific matters, chemistry, manufacturing, and controls).

(4) Subject to paragraph (5), the Secretary shall approve an application for a drug unless the Secretary finds--

(A) the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity;

(B) information submitted with the application is insufficient to show that each of the proposed conditions of use have been previously approved for the listed drug referred to in the application;

(C)(i) if the listed drug has only one active ingredient, information submitted with the application is insufficient to show that the active ingredient is the same as that of the listed drug;

(ii) if the listed drug has more than one active ingredient, information submitted with the application is insufficient to show that the active ingredients are the same as the active ingredients of the listed drug, or

(iii) if the listed drug has more than one active ingredient and if the application is for a drug which has an active ingredient different from the listed drug, information submitted with the application is insufficient to show--

(I) that the other active ingredients are the same as the active ingredients of the listed drug, or

(II) that the different active ingredient is an active ingredient of a listed drug or a drug which does not meet the requirements of section 321(p) of this title,

or no petition to file an application for the drug with the different ingredient was approved under paragraph (2)(C);

(D)(i) if the application is for a drug whose route of administration, dosage form, or strength of the drug is the same as the route of administration, dosage form, or strength of the listed drug referred to in the application, information submitted in the application is insufficient to show that the route of administration, dosage form, or strength is the same as that of the listed drug, or

(ii) if the application is for a drug whose route of administration, dosage form, or strength of the drug is different from that of the listed drug referred to in the application, no petition to file an application for the drug with the different route of administration, dosage form, or strength was approved under paragraph (2)(C);

(E) if the application was filed pursuant to the approval of a petition under paragraph (2)(C), the application did not contain the information required by the Secretary respecting the active ingredient, route of administration, dosage form, or strength which is not the same;

(F) information submitted in the application is insufficient to show that the drug is bioequivalent to the listed drug referred to in the application or, if the application was filed pursuant to a petition approved under paragraph (2)(C), information submitted in the application is insufficient to show that the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug referred to in paragraph (2)(A)(i) and that the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in such paragraph;

(G) information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the application except for changes required because of differences approved under a petition filed under paragraph (2)(C) or because the drug and the listed drug are produced or distributed by different manufacturers;

(H) information submitted in the application or any other information available to the Secretary shows that (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included;

(I) the approval under subsection (c) of this section of the listed drug referred to in the application under this subsection has been withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section, the Secretary has published a notice of opportunity for hearing to withdraw approval of the listed drug under subsection (c) of this section for grounds described in the first sentence of subsection (e) of this section, the approval under this subsection of the listed drug referred to in the application under this subsection has been withdrawn or suspended under paragraph (6), or the Secretary has determined that the listed drug has been withdrawn from sale for safety or effectiveness reasons;

(J) the application does not meet any other requirement of paragraph (2)(A); or

(K) the application contains an untrue statement of material fact.

(5)(A) Within one hundred and eighty days of the initial receipt of an application under paragraph (2) or within such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall approve or disapprove the application.

(B) The approval of an application submitted under paragraph (2) shall be made effective on the last applicable date determined by applying the following to each certification made under paragraph (2)(A)(vii):

(i) If the applicant only made a certification described in subclause (I) or (II) of paragraph (2)(A)(vii) or in both such subclauses, the approval may be made effective immediately.

(ii) If the applicant made a certification described in subclause (III) of paragraph (2)(A)(vii), the approval may be made effective on the date certified under subclause (III).

(iii) If the applicant made a certification described in subclause (IV) of paragraph (2)(A)(vii), the approval shall be made effective immediately unless, before the expiration of 45 days after the date on which the notice described in paragraph (2)(B)

is received, an action is brought for infringement of the patent that is the subject of the certification and for which information was submitted to the Secretary under subsection (b)(1) or (c)(2) of this section before the date on which the application (excluding an amendment or supplement to the application), which the Secretary later determines to be substantially complete, was submitted. If such an action is brought before the expiration of such days, the approval shall be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under paragraph (2)(B)(i) or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that--

(I) if before the expiration of such period the district court decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the approval shall be made effective on--

(aa) the date on which the court enters judgment reflecting the decision; or

(bb) the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed;

(II) if before the expiration of such period the district court decides that the patent has been infringed--

(aa) if the judgment of the district court is appealed, the approval shall be made effective on--

(AA) the date on which the court of appeals decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity); or

(BB) the date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid or not infringed; or

(bb) if the judgment of the district court is not appealed or is affirmed, the approval shall be made effective on the date specified by the district court in a court order under section 271(e)(4)(A) of Title 35;

(III) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not infringed, the approval shall be made effective as provided in subclause (I); or

(IV) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent has been infringed, the approval shall be made effective as provided in subclause (II).

In such an action, each of the parties shall reasonably cooperate in expediting the action.

(iv) 180-day exclusivity period

(I) Effectiveness of application

Subject to subparagraph (D), if the application contains a certification described in paragraph (2)(A)(vii)(IV) and is for a drug for which a first applicant has submitted an application containing such a certification, the application shall be made effective on the date that is 180 days after the date of the first commercial marketing of the drug (including the commercial marketing of the listed drug) by any first applicant.

(II) Definitions

In this paragraph:

(aa) 180-day exclusivity period

The term "180-day exclusivity period" means the 180-day period ending on the day before the date on which an application submitted by an applicant other than a first applicant could become effective under this clause.

(bb) First applicant

As used in this subsection, the term "first applicant" means an applicant that, on the first day on which a substantially complete application containing a certification described in paragraph (2)(A)(vii)(IV) is submitted for approval of a drug, submits a substantially complete application that contains and lawfully maintains a certification described in paragraph (2)(A)(vii)(IV) for the drug.

(cc) Substantially complete application

As used in this subsection, the term "substantially complete application" means an application under this subsection that on its face is sufficiently complete to permit a substantive review and contains all the information required by paragraph (2)(A).

(dd) Tentative approval

(AA) In general

The term "tentative approval" means notification to an applicant by the Secretary that an application under this subsection meets the requirements of paragraph (2)(A), but cannot receive effective approval because the application does not meet the requirements of this subparagraph, there is a period of exclusivity for the listed drug under subparagraph (F) or section 355a of this title, or there is a 7-year period of exclusivity for the listed drug under section 360cc of this title.

(BB) Limitation

A drug that is granted tentative approval by the Secretary is not an approved drug and shall not have an effective approval until the Secretary issues an approval after any necessary additional review of the application.

(C) Civil action to obtain patent certainty

(i) Declaratory judgment absent infringement action

(I) In general

No action may be brought under section 2201 of Title 28, by an applicant under paragraph (2) for a declaratory judgment with respect to a patent which is the subject of the certification referred to in subparagraph (B)(iii) unless--

(aa) the 45-day period referred to in such subparagraph has expired;

(bb) neither the owner of such patent nor the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brought a civil action against the applicant for infringement of the patent before the expiration of such period; and

(cc) in any case in which the notice provided under paragraph (2)(B) relates to noninfringement, the notice was accompanied by a document described in subclause (III).

(II) Filing of civil action

If the conditions described in items (aa), (bb), and as applicable, (cc) of subclause (I) have been met, the applicant referred to in such subclause may, in accordance with section 2201 of Title 28, bring a civil action under such section against the owner or holder referred to in such subclause (but not against any owner or holder that has brought such a civil action against the applicant, unless that civil action was dismissed without prejudice) for a declaratory judgment that the patent is invalid or will not be infringed by the drug for which the applicant seeks approval, except that such civil action may be brought for a declaratory judgment that the patent will not be infringed only in a case in which the condition described in subclause (I)(cc) is applicable. A civil action referred to in this subclause shall be brought in the judicial district where the defendant has its principal place of business or a regular and established place of business.

(III) Offer of confidential access to application

For purposes of subclause (I)(cc), the document described in this subclause is a document providing an offer of confidential access to the application that is in the custody of the applicant under paragraph (2) for the purpose of determining whether an action referred to in subparagraph (B)(iii) should be brought. The document providing the offer of confidential access shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms

of an enforceable contract. Any person provided an offer of confidential access shall review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV) and for no other purpose, and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the applicant to remove any information of no relevance to any issue of patent infringement.

(ii) Counterclaim to infringement action

(I) In general

If an owner of the patent or the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) of this section on the ground that the patent does not claim either--

(aa) the drug for which the application was approved; or

(bb) an approved method of using the drug.

(II) No independent cause of action

Subclause (I) does not authorize the assertion of a claim described in subclause (I) in any civil action or proceeding other than a counterclaim described in subclause (I).

(iii) No damages

An applicant shall not be entitled to damages in a civil action under clause (i) or a counterclaim under clause (ii).

(D) Forfeiture of 180-day exclusivity period

(i) Definition of forfeiture event

In this subparagraph, the term “forfeiture event”, with respect to an application under this subsection, means the occurrence of any of the following:

(I) Failure to market

The first applicant fails to market the drug by the later of--

(aa) the earlier of the date that is--

(AA) 75 days after the date on which the approval of the application of the first applicant is made effective under subparagraph (B)(iii); or

(BB) 30 months after the date of submission of the application of the first applicant; or

(bb) with respect to the first applicant or any other applicant (which other applicant has received tentative approval), the date that is 75 days after the date as of which, as to each of the patents with respect to which the first applicant submitted and lawfully maintained a certification qualifying the first applicant for the 180-day exclusivity period under subparagraph (B)(iv), at least 1 of the following has occurred:

(AA) In an infringement action brought against that applicant with respect to the patent or in a declaratory judgment action brought by that applicant with respect to the patent, a court enters a final decision from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken that the patent is invalid or not infringed.

(BB) In an infringement action or a declaratory judgment action described in subitem (AA), a court signs a settlement order or consent decree that enters a final judgment that includes a finding that the patent is invalid or not infringed.

(CC) The patent information submitted under subsection (b) or (c) of this section is withdrawn by the holder of the application approved under subsection (b) of this section.

(II) Withdrawal of application

The first applicant withdraws the application or the Secretary considers the application to have been withdrawn as a result of a determination by the Secretary that the application does not meet the requirements for approval under paragraph (4).

(III) Amendment of certification

The first applicant amends or withdraws the certification for all of the patents with respect to which that applicant submitted a certification qualifying the applicant for the 180-day exclusivity period.

(IV) Failure to obtain tentative approval

The first applicant fails to obtain tentative approval of the application within 30 months after the date on which the application is filed, unless the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed.

(V) Agreement with another applicant, the listed drug application holder, or a patent owner

The first applicant enters into an agreement with another applicant under this subsection for the drug, the holder of the application for the listed drug, or an owner of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV), the Federal Trade Commission or the Attorney General files a complaint, and there is a final decision of the Federal Trade Commission or the court with regard to the complaint from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken that the agreement has violated the antitrust laws (as defined in section 12 of Title 15, except that the term includes section 45 of Title 15 to the extent that that section applies to unfair methods of competition).

(VI) Expiration of all patents

All of the patents as to which the applicant submitted a certification qualifying it for the 180-day exclusivity period have expired.

(ii) Forfeiture

The 180-day exclusivity period described in subparagraph (B)(iv) shall be forfeited by a first applicant if a forfeiture event occurs with respect to that first applicant.

(iii) Subsequent applicant

If all first applicants forfeit the 180-day exclusivity period under clause (ii)--

(I) approval of any application containing a certification described in paragraph (2)(A)(vii)(IV) shall be made effective in accordance with subparagraph (B)(iii); and

(II) no applicant shall be eligible for a 180-day exclusivity period.

(E) If the Secretary decides to disapprove an application, the Secretary shall give the applicant notice of an opportunity for a hearing before the Secretary on the question of whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(F)(i) If an application (other than an abbreviated new drug application) submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted effective before the expiration of ten years from the date of the approval of the application under subsection (b) of this section.

(ii) If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after

September 24, 1984, no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b) of this section, except that such an application may be submitted under this subsection after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in subclause (IV) of paragraph (2)(A)(vii). The approval of such an application shall be made effective in accordance with subparagraph (B) except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (B)(iii) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

(iii) If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) of this section for such drug.

(iv) If a supplement to an application approved under subsection (b) of this section is approved after September 24, 1984, and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under this subsection for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) of this section.

(v) If an application (or supplement to an application) submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted or which refers to a change approved in a supplement to the subsection (b) application effective before the expiration of two years from September 24, 1984.

(6) If a drug approved under this subsection refers in its approved application to a drug the approval of which was withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section or was withdrawn or suspended under this paragraph or which, as determined by the Secretary, has been withdrawn from sale for safety or effectiveness reasons, the approval of the drug under this subsection shall be withdrawn or suspended--

(A) for the same period as the withdrawal or suspension under subsection (e) of this section or this paragraph, or

(B) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary determines that the withdrawal from sale is not for safety or effectiveness reasons.

(7)(A)(i) Within sixty days of September 24, 1984, the Secretary shall publish and make available to the public--

(I) a list in alphabetical order of the official and proprietary name of each drug which has been approved for safety and effectiveness under subsection (c) of this section before September 24, 1984;

(II) the date of approval if the drug is approved after 1981 and the number of the application which was approved; and

(III) whether in vitro or in vivo bioequivalence studies, or both such studies, are required for applications filed under this subsection which will refer to the drug published.

(ii) Every thirty days after the publication of the first list under clause (i) the Secretary shall revise the list to include each drug which has been approved for safety and effectiveness under subsection (c) of this section or approved under this subsection during the thirty-day period.

(iii) When patent information submitted under subsection (b) or (c) of this section respecting a drug included on the list is to be published by the Secretary, the Secretary shall, in revisions made under clause (ii), include such information for such drug.

(B) A drug approved for safety and effectiveness under subsection (c) of this section or approved under this subsection shall, for purposes of this subsection, be considered to have been published under subparagraph (A) on the date of its approval or September 24, 1984, whichever is later.

(C) If the approval of a drug was withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section or was withdrawn or suspended under paragraph (6) or if the Secretary determines that a drug has been withdrawn from sale for safety or effectiveness reasons, it may not be published in the list under subparagraph (A) or, if the withdrawal or suspension occurred after its publication in such list, it shall be immediately removed from such list--

(i) for the same period as the withdrawal or suspension under subsection (e) of this section or paragraph (6), or

(ii) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary determines that the withdrawal from sale is not for safety or effectiveness reasons.

A notice of the removal shall be published in the Federal Register.

(8) For purposes of this subsection:

(A)(i) The term "bioavailability" means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.

(ii) For a drug that is not intended to be absorbed into the bloodstream, the Secretary may assess bioavailability by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action.

(B) A drug shall be considered to be bioequivalent to a listed drug if--

(i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or

(ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

(C) For a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.

(9) The Secretary shall, with respect to each application submitted under this subsection, maintain a record of--

(A) the name of the applicant,

(B) the name of the drug covered by the application,

(C) the name of each person to whom the review of the chemistry of the application was assigned and the date of such assignment, and

(D) the name of each person to whom the bioequivalence review for such application was assigned and the date of such assignment.

The information the Secretary is required to maintain under this paragraph with respect to an application submitted under this subsection shall be made available to the public after the approval of such application.

(10)(A) If the proposed labeling of a drug that is the subject of an application under this subsection differs from the listed drug due to a labeling revision described under clause (i), the drug that is the subject of such application shall, notwithstanding any other provision of this chapter, be eligible for approval and shall not be considered misbranded under section 352 of this title if--

(i) the application is otherwise eligible for approval under this subsection but for expiration of patent, an exclusivity period, or of a delay in approval described in paragraph (5)(B)(iii), and a revision to the labeling of the listed drug has been approved by the Secretary within 60 days of such expiration;

(ii) the labeling revision described under clause (i) does not include a change to the "Warnings" section of the labeling;

(iii) the sponsor of the application under this subsection agrees to submit revised labeling of the drug that is the subject of such application not later than 60 days after the notification of any changes to such labeling required by the Secretary; and

(iv) such application otherwise meets the applicable requirements for approval under this subsection.

(B) If, after a labeling revision described in subparagraph (A)(i), the Secretary determines that the continued presence in interstate commerce of the labeling of the listed drug (as in effect before the revision described in subparagraph (A)(i)) adversely impacts the safe use of the drug, no application under this subsection shall be eligible for approval with such labeling.

(k) Records and reports; required information; regulations and orders; access to records

(1) In the case of any drug for which an approval of an application filed under subsection (b) or (j) of this section is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) of this section. Regulations and orders issued under this subsection and under subsection (i) of this section shall have due regard for the professional ethics of the medical profession and the interests of patients and shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulations or orders are applicable, of similar information received or otherwise obtained by the Secretary.

(2) Every person required under this section to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

(3) Active postmarket risk identification

(A) Definition

In this paragraph, the term "data" refers to information with respect to a drug approved under this section or under section 262 of Title 42, including claims data, patient survey data, standardized analytic files that allow for the pooling and analysis of data from disparate data environments, and any other data deemed appropriate by the Secretary.

(B) Development of postmarket risk identification and analysis methods

The Secretary shall, not later than 2 years after September 27, 2007, in collaboration with public, academic, and private entities--

(i) develop methods to obtain access to disparate data sources including the data sources specified in subparagraph (C);

(ii) develop validated methods for the establishment of a postmarket risk identification and analysis system to link and analyze safety data from multiple sources, with the goals of including, in aggregate--

(I) at least 25,000,000 patients by July 1, 2010; and

(II) at least 100,000,000 patients by July 1, 2012; and

(iii) convene a committee of experts, including individuals who are recognized in the field of protecting data privacy and security, to make recommendations to the Secretary on the development of tools and methods for the ethical and scientific uses for, and communication of, postmarketing data specified under subparagraph (C), including recommendations on the development of effective research methods for the study of drug safety questions.

(C) Establishment of the postmarket risk identification and analysis system

(i) In general

The Secretary shall, not later than 1 year after the development of the risk identification and analysis methods under subparagraph (B), establish and maintain procedures--

(I) for risk identification and analysis based on electronic health data, in compliance with the regulations promulgated under section 264(c) of the Health Insurance Portability and Accountability Act of 1996, and in a manner that does not disclose individually identifiable health information in violation of paragraph (4)(B);

(II) for the reporting (in a standardized form) of data on all serious adverse drug experiences (as defined in section 355-1(b) of this title) submitted to the Secretary under paragraph (1), and those adverse events submitted by patients, providers, and drug sponsors, when appropriate;

(III) to provide for active adverse event surveillance using the following data sources, as available:

(aa) Federal health-related electronic data (such as data from the Medicare program and the health systems of the Department of Veterans Affairs);

(bb) private sector health-related electronic data (such as pharmaceutical purchase data and health insurance claims data); and

(cc) other data as the Secretary deems necessary to create a robust system to identify adverse events and potential drug safety signals;

(IV) to identify certain trends and patterns with respect to data accessed by the system;

(V) to provide regular reports to the Secretary concerning adverse event trends, adverse event patterns, incidence and prevalence of adverse events, and other information the Secretary determines appropriate, which may include data on comparative national adverse event trends; and

(VI) to enable the program to export data in a form appropriate for further aggregation, statistical analysis, and reporting.

(ii) Timeliness of reporting

The procedures established under clause (i) shall ensure that such data are accessed, analyzed, and reported in a timely, routine, and systematic manner, taking into consideration the need for data completeness, coding, cleansing, and standardized analysis and transmission.

(iii) Private sector resources

To ensure the establishment of the active postmarket risk identification and analysis system under this subsection not later than 1 year after the development of the risk identification and analysis methods under subparagraph (B), as required under clause (i), the Secretary may, on a temporary or permanent basis, implement systems or products developed by private entities.

(iv) Complementary approaches

To the extent the active postmarket risk identification and analysis system under this subsection is not sufficient to gather data and information relevant to a priority drug safety question, the Secretary shall develop, support, and participate in complementary approaches to gather and analyze such data and information, including--

(I) approaches that are complementary with respect to assessing the safety of use of a drug in domestic populations not included, or underrepresented, in the trials used to approve the drug (such as older people, people with comorbidities, pregnant women, or children); and

(II) existing approaches such as the Vaccine Adverse Event Reporting System and the Vaccine Safety Datalink or successor databases.

(v) Authority for contracts

The Secretary may enter into contracts with public and private entities to fulfill the requirements of this subparagraph.

(4) Advanced analysis of drug safety data

(A) Purpose

The Secretary shall establish collaborations with public, academic, and private entities, which may include the Centers for Education and Research on Therapeutics under section 299b-1 of Title 42, to provide for advanced analysis of drug safety data described in paragraph (3)(C) and other information that is publicly available or is provided by the Secretary, in order to--

(i) improve the quality and efficiency of postmarket drug safety risk-benefit analysis;

(ii) provide the Secretary with routine access to outside expertise to study advanced drug safety questions; and

(iii) enhance the ability of the Secretary to make timely assessments based on drug safety data.

(B) Privacy

Such analysis shall not disclose individually identifiable health information when presenting such drug safety signals and trends or when responding to inquiries regarding such drug safety signals and trends.

(C) Public process for priority questions

At least biannually, the Secretary shall seek recommendations from the Drug Safety and Risk Management Advisory Committee (or any successor committee) and from other advisory committees, as appropriate, to the Food and Drug Administration on--

(i) priority drug safety questions; and

(ii) mechanisms for answering such questions, including through--

(I) active risk identification under paragraph (3); and

(II) when such risk identification is not sufficient, postapproval studies and clinical trials under subsection (o)(3).

(D) Procedures for the development of drug safety collaborations

(i) In general

Not later than 180 days after the date of the establishment of the active postmarket risk identification and analysis system under this subsection, the Secretary shall establish and implement procedures under which the Secretary may routinely contract with one or more qualified entities to--

(I) classify, analyze, or aggregate data described in paragraph (3)(C) and information that is publicly available or is provided by the Secretary;

(II) allow for prompt investigation of priority drug safety questions, including--

(aa) unresolved safety questions for drugs or classes of drugs; and

(bb) for a newly-approved drugs, [2] safety signals from clinical trials used to approve the drug and other preapproval trials; rare, serious drug side effects; and the safety of use in domestic populations not included, or underrepresented, in the trials used to approve the drug (such as older people, people with comorbidities, pregnant women, or children);

(III) perform advanced research and analysis on identified drug safety risks;

(IV) focus postapproval studies and clinical trials under subsection (o)(3) more effectively on cases for which reports under paragraph (1) and other safety signal detection is not sufficient to resolve whether there is an elevated risk of a serious adverse event associated with the use of a drug; and

(V) carry out other activities as the Secretary deems necessary to carry out the purposes of this paragraph.

(ii) Request for specific methodology

The procedures described in clause (i) shall permit the Secretary to request that a specific methodology be used by the qualified entity. The qualified entity shall work with the Secretary to finalize the methodology to be used.

(E) Use of analyses

The Secretary shall provide the analyses described in this paragraph, including the methods and results of such analyses, about a drug to the sponsor or sponsors of such drug.

(F) Qualified entities

(i) In general

The Secretary shall enter into contracts with a sufficient number of qualified entities to develop and provide information to the Secretary in a timely manner.

(ii) Qualification

The Secretary shall enter into a contract with an entity under clause (i) only if the Secretary determines that the entity has a significant presence in the United States and has one or more of the following qualifications:

(I) The research, statistical, epidemiologic, or clinical capability and expertise to conduct and complete the activities under this paragraph, including the capability and expertise to provide the Secretary de-identified data consistent with the requirements of this subsection.

(II) An information technology infrastructure in place to support electronic data and operational standards to provide security for such data.

(III) Experience with, and expertise on, the development of drug safety and effectiveness research using electronic population data.

(IV) An understanding of drug development or risk/benefit balancing in a clinical setting.

(V) Other expertise which the Secretary deems necessary to fulfill the activities under this paragraph.

(G) Contract requirements

Each contract with a qualified entity under subparagraph (F)(i) shall contain the following requirements:

(i) Ensuring privacy

The qualified entity shall ensure that the entity will not use data under this subsection in a manner that--

(I) violates the regulations promulgated under section 264(c) of the Health Insurance Portability and Accountability Act of 1996;

(II) violates sections 552 or 552a of Title 5 with regard to the privacy of individually-identifiable beneficiary health information; or

(III) discloses individually identifiable health information when presenting drug safety signals and trends or when responding to inquiries regarding drug safety signals and trends.

Nothing in this clause prohibits lawful disclosure for other purposes.

(ii) Component of another organization

If a qualified entity is a component of another organization--

(I) the qualified entity shall establish appropriate security measures to maintain the confidentiality and privacy of such data; and

(II) the entity shall not make an unauthorized disclosure of such data to the other components of the organization in breach of such confidentiality and privacy requirement.

(iii) Termination or nonrenewal

If a contract with a qualified entity under this subparagraph is terminated or not renewed, the following requirements shall apply:

(I) Confidentiality and privacy protections

The entity shall continue to comply with the confidentiality and privacy requirements under this paragraph with respect to all data disclosed to the entity.

(II) Disposition of data

The entity shall return any data disclosed to such entity under this subsection to which it would not otherwise have access or, if returning the data is not practicable, destroy the data.

(H) Competitive procedures

The Secretary shall use competitive procedures (as defined in section 132 of Title 41) to enter into contracts under subparagraph (G).

(I) Review of contract in the event of a merger or acquisition

The Secretary shall review the contract with a qualified entity under this paragraph in the event of a merger or acquisition of the entity in order to ensure that the requirements under this paragraph will continue to be met.

(J) Coordination

In carrying out this paragraph, the Secretary shall provide for appropriate communications to the public, scientific, public health, and medical communities, and other key stakeholders, and to the extent practicable shall coordinate with the activities of private entities, professional associations, or other entities that may have sources of drug safety data.

(5) The Secretary shall--

(A) conduct regular, bi-weekly screening of the Adverse Event Reporting System database and post a quarterly report on the Adverse Event Reporting System Web site of any new safety information or potential signal of a serious risk identified by Adverse [3] Event Reporting System within the last quarter;

(B) report to Congress not later than 2 year[4] after September 27, 2007 on procedures and processes of the Food and Drug Administration for addressing ongoing post market safety issues identified by the Office of Surveillance and Epidemiology and how recommendations of the Office of Surveillance and Epidemiology are handled within the agency; and

(C) on an annual basis, review the entire backlog of postmarket safety commitments to determine which commitments require revision or should be eliminated, report to the Congress on these determinations, and assign start dates and estimated completion dates for such commitments.

(l) Public disclosure of safety and effectiveness data and action package

(1) Safety and effectiveness data and information which has been submitted in an application under subsection (b) of this section for a drug and which has not previously been disclosed to the public shall be made available to the public, upon request, unless extraordinary circumstances are shown--

(A) if no work is being or will be undertaken to have the application approved,

(B) if the Secretary has determined that the application is not approvable and all legal appeals have been exhausted,

(C) if approval of the application under subsection (c) of this section is withdrawn and all legal appeals have been exhausted,

(D) if the Secretary has determined that such drug is not a new drug, or

(E) upon the effective date of the approval of the first application under subsection (j) of this section which refers to such drug or upon the date upon which the approval of an application under subsection (j) of this section which refers to such drug could be made effective if such an application had been submitted.

(2) Action package for approval

(A) Action package

The Secretary shall publish the action package for approval of an application under subsection (b) or section 262 of title 42 on the Internet Web site of the Food and Drug Administration--

(i) not later than 30 days after the date of approval of such application for a drug no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under this section or section 262 of Title 42; and

(ii) not later than 30 days after the third request for such action package for approval received under section 552 of Title 5 for any other drug.

(B) Immediate publication of summary review

Notwithstanding subparagraph (A), the Secretary shall publish, on the Internet Web site of the Food and Drug Administration, the materials described in subparagraph (C)(iv) not later than 48 hours after the date of approval of the drug, except where such materials require redaction by the Secretary.

(C) Contents

An action package for approval of an application under subparagraph (A) shall be dated and shall include the following:

(i) Documents generated by the Food and Drug Administration related to review of the application.

(ii) Documents pertaining to the format and content of the application generated during drug development.

(iii) Labeling submitted by the applicant.

(iv) A summary review that documents conclusions from all reviewing disciplines about the drug, noting any critical issues and disagreements with the applicant and within the review team and how they were resolved, recommendations for action, and an explanation of any nonconcurrence with review conclusions.

(v) The Division Director and Office Director's decision document which includes--

(I) a brief statement of concurrence with the summary review;

(II) a separate review or addendum to the review if disagreeing with the summary review; and

(III) a separate review or addendum to the review to add further analysis.

(vi) Identification by name of each officer or employee of the Food and Drug Administration who--

(I) participated in the decision to approve the application; and

(II) consents to have his or her name included in the package.

(D) Review

A scientific review of an application is considered the work of the reviewer and shall not be altered by management or the reviewer once final.

(E) Confidential information

This paragraph does not authorize the disclosure of any trade secret, confidential commercial or financial information, or other matter listed in section 552(b) of Title 5.

(m) "Patent" defined

For purposes of this section, the term "patent" means a patent issued by the United States Patent and Trademark Office.

(n) Scientific advisory panels

(1) For the purpose of providing expert scientific advice and recommendations to the Secretary regarding a clinical investigation of a drug or the approval for marketing of a drug under this section or section 262 of Title 42, the Secretary shall establish panels of experts or use panels of experts established before November 21, 1997, or both.

(2) The Secretary may delegate the appointment and oversight authority granted under section 394 of this title to a director of a center or successor entity within the Food and Drug Administration.

(3) The Secretary shall make appointments to each panel established under paragraph (1) so that each panel shall consist of--

(A) members who are qualified by training and experience to evaluate the safety and effectiveness of the drugs to be referred to the panel and who, to the extent feasible, possess skill and experience in the development, manufacture, or utilization of such drugs;

(B) members with diverse expertise in such fields as clinical and administrative medicine, pharmacy, pharmacology, pharmacoeconomics, biological and physical sciences, and other related professions;

(C) a representative of consumer interests, and a representative of interests of the drug manufacturing industry not directly affected by the matter to be brought before the panel; and

(D) two or more members who are specialists or have other expertise in the particular disease or condition for which the drug under review is proposed to be indicated.

Scientific, trade, and consumer organizations shall be afforded an opportunity to nominate individuals for appointment to the panels. No individual who is in the regular full-time employ of the United States and engaged in the administration of this chapter may be a voting member of any panel. The Secretary shall designate one of the members of each panel to serve as chairman thereof.

(4) The Secretary shall, as appropriate, provide education and training to each new panel member before such member participates in a panel's activities, including education regarding requirements under this chapter and related regulations of the Secretary, and the administrative processes and procedures related to panel meetings.

(5) Panel members (other than officers or employees of the United States), while attending meetings or conferences of a panel or otherwise engaged in its business, shall be entitled to receive compensation for each day so engaged, including traveltime, at rates to be fixed by the Secretary, but not to exceed the daily equivalent of the rate in effect for positions classified above grade GS-15 of the General Schedule. While serving away from their homes or regular places of business, panel members may be allowed travel expenses (including per diem in lieu of subsistence) as authorized by section 5703 of Title 5, for persons in the Government service employed intermittently.

(6) The Secretary shall ensure that scientific advisory panels meet regularly and at appropriate intervals so that any matter to be reviewed by such a panel can be presented to the panel not more than 60 days after the matter is ready for such review. Meetings of the panel may be held using electronic communication to convene the meetings.

(7) Within 90 days after a scientific advisory panel makes recommendations on any matter under its review, the Food and Drug Administration official responsible for the matter shall review the conclusions and recommendations of the panel, and notify the affected persons of the final decision on the matter, or of the reasons that no such decision has been reached. Each such final decision shall be documented including the rationale for the decision.

(o) Postmarket studies and clinical trials; labeling

(1) In general

A responsible person may not introduce or deliver for introduction into interstate commerce the new drug involved if the person is in violation of a requirement established under paragraph (3) or (4) with respect to the drug.

(2) Definitions

For purposes of this subsection:

(A) Responsible person

The term “responsible person” means a person who--

(i) has submitted to the Secretary a covered application that is pending; or

(ii) is the holder of an approved covered application.

(B) Covered application

The term “covered application” means--

(i) an application under subsection (b) for a drug that is subject to section 353(b) of this title; and

(ii) an application under section 262 of Title 42.

(C) New safety information; serious risk

The terms "new safety information", "serious risk", and "signal of a serious risk" have the meanings given such terms in section 355-1(b) of this title.

(3) Studies and clinical trials

(A) In general

For any or all of the purposes specified in subparagraph (B), the Secretary may, subject to subparagraph (D), require a responsible person for a drug to conduct a postapproval study or studies of the drug, or a postapproval clinical trial or trials of the drug, on the basis of scientific data deemed appropriate by the Secretary, including information regarding chemically-related or pharmacologically-related drugs.

(B) Purposes of study or clinical trial

The purposes referred to in this subparagraph with respect to a postapproval study or postapproval clinical trial are the following:

(i) To assess a known serious risk related to the use of the drug involved.

(ii) To assess signals of serious risk related to the use of the drug.

(iii) To identify an unexpected serious risk when available data indicates the potential for a serious risk.

(C) Establishment of requirement after approval of covered application

The Secretary may require a postapproval study or studies or postapproval clinical trial or trials for a drug for which an approved covered application is in effect as of the date on which the Secretary seeks to establish such requirement only if the Secretary becomes aware of new safety information.

(D) Determination by Secretary

(i) Postapproval studies

The Secretary may not require the responsible person to conduct a study under this paragraph, unless the Secretary makes a determination that the reports under subsection (k)(1) and the active postmarket risk identification and analysis system as available under subsection (k)(3) will not be sufficient to meet the purposes set forth in subparagraph (B).

(ii) Postapproval clinical trials

The Secretary may not require the responsible person to conduct a clinical trial under this paragraph, unless the Secretary makes a determination that a postapproval study or studies will not be sufficient to meet the purposes set forth in subparagraph (B).

(E) Notification; timetables; periodic reports

(i) Notification

The Secretary shall notify the responsible person regarding a requirement under this paragraph to conduct a postapproval study or clinical trial by the target dates for communication of feedback from the review team to the responsible person regarding proposed labeling and postmarketing study commitments as set forth in the letters described in section 101(c) of the Food and Drug Administration Amendments Act of 2007.

(ii) Timetable; periodic reports

For each study or clinical trial required to be conducted under this paragraph, the Secretary shall require that the responsible person submit a timetable for completion of the study or clinical trial. With respect to each study required to be conducted under this paragraph or otherwise undertaken by the responsible person to investigate a safety issue, the Secretary shall require the responsible person to periodically report to the Secretary on the status of such study including whether any difficulties in completing the study have been encountered. With respect to each clinical trial required to be conducted under this paragraph or otherwise undertaken by the responsible person to investigate a safety issue, the Secretary shall require the responsible person to periodically report to the Secretary on the status of such clinical trial including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to the requirements under section 282(j) of Title 42. If the responsible person fails to comply with such timetable or violates any other requirement of this subparagraph, the responsible person shall be considered in violation of this subsection, unless the responsible person demonstrates good cause for such noncompliance or such other violation. The Secretary shall determine what constitutes good cause under the preceding sentence.

(F) Dispute resolution

The responsible person may appeal a requirement to conduct a study or clinical trial under this paragraph using dispute resolution procedures established by the Secretary in regulation and guidance.

(4) Safety labeling changes requested by Secretary

(A) New safety information

If the Secretary becomes aware of new safety information that the Secretary believes should be included in the labeling of the drug, the Secretary shall promptly notify the responsible person or, if the same drug approved under subsection (b) is not currently marketed, the holder of an approved application under subsection (j).

(B) Response to notification

Following notification pursuant to subparagraph (A), the responsible person or the holder of the approved application under subsection (j) shall within 30 days--

(i) submit a supplement proposing changes to the approved labeling to reflect the new safety information, including changes to boxed warnings, contraindications, warnings, precautions, or adverse reactions; or

(ii) notify the Secretary that the responsible person or the holder of the approved application under subsection (j) does not believe a labeling change is warranted and submit a statement detailing the reasons why such a change is not warranted.

(C) Review

Upon receipt of such supplement, the Secretary shall promptly review and act upon such supplement. If the Secretary disagrees with the proposed changes in the supplement or with the statement setting forth the reasons why no labeling change is necessary, the Secretary shall initiate discussions to reach agreement on whether the labeling for the drug should be modified to reflect the new safety information, and if so, the contents of such labeling changes.

(D) Discussions

Such discussions shall not extend for more than 30 days after the response to the notification under subparagraph (B), unless the Secretary determines an extension of such discussion period is warranted.

(E) Order

Within 15 days of the conclusion of the discussions under subparagraph (D), the Secretary may issue an order directing the responsible person or the holder of the approved application under subsection (j) to make such a labeling change as the Secretary deems appropriate to address the new safety information. Within 15 days of such an order, the responsible person or the holder of the approved application under subsection (j) shall submit a supplement containing the labeling change.

(F) Dispute resolution

Within 5 days of receiving an order under subparagraph (E), the responsible person or the holder of the approved application under subsection (j) may appeal using dispute resolution procedures established by the Secretary in regulation and guidance.

(G) Violation

If the responsible person or the holder of the approved application under subsection (j) has not submitted a supplement within 15 days of the date of such order under subparagraph (E), and there is no appeal or dispute resolution proceeding pending, the responsible person or holder shall be considered to be in violation of this subsection. If at the conclusion of any dispute resolution procedures the Secretary determines that a supplement must be submitted and such a supplement

is not submitted within 15 days of the date of that determination, the responsible person or holder shall be in violation of this subsection.

(H) Public health threat

Notwithstanding subparagraphs (A) through (F), if the Secretary concludes that such a labeling change is necessary to protect the public health, the Secretary may accelerate the timelines in such subparagraphs.

(I) Rule of construction

This paragraph shall not be construed to affect the responsibility of the responsible person or the holder of the approved application under subsection (j) to maintain its label in accordance with existing requirements, including subpart B of part 201 and sections 314.70 and 601.12 of title 21, Code of Federal Regulations (or any successor regulations).

(5) Non-delegation

Determinations by the Secretary under this subsection for a drug shall be made by individuals at or above the level of individuals empowered to approve a drug (such as division directors within the Center for Drug Evaluation and Research).

(p) Risk evaluation and mitigation strategy

(1) In general

A person may not introduce or deliver for introduction into interstate commerce a new drug if--

(A)(i) the application for such drug is approved under subsection (b) or (j) and is subject to section 353(b) of this title; or

(ii) the application for such drug is approved under section 262 of Title 42; and

(B) a risk evaluation and mitigation strategy is required under section 355-1 of this title with respect to the drug and the person fails to maintain compliance with the requirements of the approved strategy or with other requirements under section 355-1 of this title, including requirements regarding assessments of approved strategies.

(2) Certain postmarket studies

The failure to conduct a postmarket study under section 356 of this title, subpart H of part 314, or subpart E of part 601 of title 21, Code of Federal Regulations (or any successor regulations), is deemed to be a violation of paragraph (1).

(q) Petitions and civil actions regarding approval of certain applications

(1) In general

(A) Determination

The Secretary shall not delay approval of a pending application submitted under subsection (b)(2) or (j) of this section or section 262(k) of Title 42 because of any request to take any form of action relating to the application, either before or during consideration of the request, unless--

(i) the request is in writing and is a petition submitted to the Secretary pursuant to section 10.30 or 10.35 of title 21, Code of Federal Regulations (or any successor regulations); and

(ii) the Secretary determines, upon reviewing the petition, that a delay is necessary to protect the public health.

Consideration of the petition shall be separate and apart from review and approval of any application.

(B) Notification

If the Secretary determines under subparagraph (A) that a delay is necessary with respect to an application, the Secretary shall provide to the applicant, not later than 30 days after making such determination, the following information:

(i) Notification of the fact that a determination under subparagraph (A) has been made.

(ii) If applicable, any clarification or additional data that the applicant should submit to the docket on the petition to allow the Secretary to review the petition promptly.

(iii) A brief summary of the specific substantive issues raised in the petition which form the basis of the determination.

(C) Format

The information described in subparagraph (B) shall be conveyed via either, at the discretion of the Secretary--

(i) a document; or

(ii) a meeting with the applicant involved.

(D) Public disclosure

Any information conveyed by the Secretary under subparagraph (C) shall be considered part of the application and shall be subject to the disclosure requirements applicable to information in such application.

(E) Denial based on intent to delay

If the Secretary determines that a petition or a supplement to the petition was submitted with the primary purpose of delaying the approval of an application and the petition does not on its face raise valid scientific or regulatory issues, the Secretary may deny the petition at any point based on such determination. The Secretary may issue guidance to describe the factors that will be used to determine under this subparagraph whether a petition is submitted with the primary purpose of delaying the approval of an application.

(F) Final agency action

The Secretary shall take final agency action on a petition not later than 150 days after the date on which the petition is submitted. The Secretary shall not extend such period for any reason, including--

(i) any determination made under subparagraph (A);

(ii) the submission of comments relating to the petition or supplemental information supplied by the petitioner; or

(iii) the consent of the petitioner.

(G) Extension of 30-month period

If the filing of an application resulted in first-applicant status under subsection (j)(5)(D)(i)(IV) and approval of the application was delayed because of a petition, the 30-month period under such subsection is deemed to be extended by a period of time equal to the period beginning on the date on which the Secretary received the petition and ending on the date of final agency action on the petition (inclusive of such beginning and ending dates), without regard to whether the Secretary grants, in whole or in part, or denies, in whole or in part, the petition.

(H) Certification

The Secretary shall not consider a petition for review unless the party submitting such petition does so in written form and the subject document is signed and contains the following certification: “I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: _____. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: _____. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.”, with the date on which such information first became known to such party and the names of such persons or organizations inserted in the first and second blank space, respectively.

(I) Verification

The Secretary shall not accept for review any supplemental information or comments on a petition unless the party submitting such information or comments does so in written form and the subject document is signed and contains the

following verification: "I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about _____. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: _____. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.", with the date on which such information first became known to the party and the names of such persons or organizations inserted in the first and second blank space, respectively.

(2) Exhaustion of administrative remedies

(A) Final agency action within 150 days

The Secretary shall be considered to have taken final agency action on a petition if--

(i) during the 150-day period referred to in paragraph (1)(F), the Secretary makes a final decision within the meaning of section 10.45(d) of title 21, Code of Federal Regulations (or any successor regulation); or

(ii) such period expires without the Secretary having made such a final decision.

(B) Dismissal of certain civil actions

If a civil action is filed against the Secretary with respect to any issue raised in the petition before the Secretary has taken final agency action on the petition within the meaning of subparagraph (A), the court shall dismiss without prejudice the action for failure to exhaust administrative remedies.

(C) Administrative record

For purposes of judicial review related to the approval of an application for which a petition under paragraph (1) was submitted, the administrative record regarding any issue raised by the petition shall include--

(i) the petition filed under paragraph (1) and any supplements and comments thereto;

(ii) the Secretary's response to such petition, if issued; and

(iii) other information, as designated by the Secretary, related to the Secretary's determinations regarding the issues raised in such petition, as long as the information was considered by the agency no later than the date of final agency action as defined under subparagraph (2)(A), and regardless of whether the Secretary responded to the petition at or before the approval of the application at issue in the petition.

(3) Annual report on delays in approvals per petitions

The Secretary shall annually submit to the Congress a report that specifies--

(A) the number of applications that were approved during the preceding 12-month period;

(B) the number of such applications whose effective dates were delayed by petitions referred to in paragraph (1) during such period;

(C) the number of days by which such applications were so delayed; and

(D) the number of such petitions that were submitted during such period.

(4) Exceptions

(A) This subsection does not apply to--

(i) a petition that relates solely to the timing of the approval of an application pursuant to subsection (j)(5)(B)(iv); or

(ii) a petition that is made by the sponsor of an application and that seeks only to have the Secretary take or refrain from taking any form of action with respect to that application.

(B) Paragraph (2) does not apply to a petition addressing issues concerning an application submitted pursuant to section 262(k) of Title 42.

(5) Definitions

(A) Application

For purposes of this subsection, the term "application" means an application submitted under subsection (b)(2) or (j) of this section or section 262(k) of Title 42.

(B) Petition

For purposes of this subsection, other than paragraph (1)(A)(i), the term "petition" means a request described in paragraph (1)(A)(i).

(r) Postmarket drug safety information for patients and providers

(1) Establishment

Not later than 1 year after September 27, 2007, the Secretary shall improve the transparency of information about drugs and allow patients and health care providers better access to information about drugs by developing and maintaining an Internet Web site that--

(A) provides links to drug safety information listed in paragraph (2) for prescription drugs that are approved under this section or licensed under section 262 of Title 42; and

(B) improves communication of drug safety information to patients and providers.

(2) Internet Web site

The Secretary shall carry out paragraph (1) by--

(A) developing and maintaining an accessible, consolidated Internet Web site with easily searchable drug safety information, including the information found on United States Government Internet Web sites, such as the United States National Library of Medicine's Daily Med and Medline Plus Web sites, in addition to other such Web sites maintained by the Secretary;

(B) ensuring that the information provided on the Internet Web site is comprehensive and includes, when available and appropriate--

(i) patient labeling and patient packaging inserts;

(ii) a link to a list of each drug, whether approved under this section or licensed under such section 262, for which a Medication Guide, as provided for under part 208 of title 21, Code of Federal Regulations (or any successor regulations), is required;

(iii) a link to the registry and results data bank provided for under subsections (i) and (j) of section 282 of Title 42;

(iv) the most recent safety information and alerts issued by the Food and Drug Administration for drugs approved by the Secretary under this section, such as product recalls, warning letters, and import alerts;

(v) publicly available information about implemented RiskMAPs and risk evaluation and mitigation strategies under subsection (o);

(vi) guidance documents and regulations related to drug safety; and

(vii) other material determined appropriate by the Secretary;

(C) providing access to summaries of the assessed and aggregated data collected from the active surveillance infrastructure under subsection (k)(3) to provide information of known and serious side-effects for drugs approved under this section or licensed under such section 262 of Title 42;

(D) preparing, by 18 months after approval of a drug or after use of the drug by 10,000 individuals, whichever is later, a summary analysis of the adverse drug reaction reports received for the drug, including identification of any new risks not previously identified, potential new risks, or known risks reported in unusual number;

(E) enabling patients, providers, and drug sponsors to submit adverse event reports through the Internet Web site;

(F) providing educational materials for patients and providers about the appropriate means of disposing of expired, damaged, or unusable medications; and

(G) supporting initiatives that the Secretary determines to be useful to fulfill the purposes of the Internet Web site.

(3) Posting of drug labeling

The Secretary shall post on the Internet Web site established under paragraph (1) the approved professional labeling and any required patient labeling of a drug approved under this section or licensed under such section 262 of Title 42 not later than 21 days after the date the drug is approved or licensed, including in a supplemental application with respect to a labeling change.

(4) Private sector resources

To ensure development of the Internet Web site by the date described in paragraph (1), the Secretary may, on a temporary or permanent basis, implement systems or products developed by private entities.

(5) Authority for contracts

The Secretary may enter into contracts with public and private entities to fulfill the requirements of this subsection.

(6) Review

The Advisory Committee on Risk Communication under section 360bbb-6 of this title shall, on a regular basis, perform a comprehensive review and evaluation of the types of risk communication information provided on the Internet Web site established under paragraph (1) and, through other means, shall identify, clarify, and define the purposes and types of information available to facilitate the efficient flow of information to patients and providers, and shall recommend ways for the Food and Drug Administration to work with outside entities to help facilitate the dispensing of risk communication information to patients and providers.

(s) Referral to advisory committee

Prior to the approval of a drug no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under this section or section 262 of Title 42, the Secretary shall--

(1) refer such drug to a Food and Drug Administration advisory committee for review at a meeting of such advisory committee; or

(2) if the Secretary does not refer such a drug to a Food and Drug Administration advisory committee prior to the approval of the drug, provide in the action letter on the application for the drug a summary of the reasons why the Secretary did not refer the drug to an advisory committee prior to approval.

(t) Database for authorized generic drugs

(1) In general

(A) Publication

The Commissioner shall--

(i) not later than 9 months after September 27, 2007, publish a complete list on the Internet Web site of the Food and Drug Administration of all authorized generic drugs (including drug trade name, brand company manufacturer, and the date the authorized generic drug entered the market); and

(ii) update the list quarterly to include each authorized generic drug included in an annual report submitted to the Secretary by the sponsor of a listed drug during the preceding 3-month period.

(B) Notification

The Commissioner shall notify relevant Federal agencies, including the Centers for Medicare & Medicaid Services and the Federal Trade Commission, when the Commissioner first publishes the information described in subparagraph (A) that the information has been published and that the information will be updated quarterly.

(2) Inclusion

The Commissioner shall include in the list described in paragraph (1) each authorized generic drug included in an annual report submitted to the Secretary by the sponsor of a listed drug after January 1, 1999.

(3) Authorized generic drug

In this section, the term “authorized generic drug” means a listed drug (as that term is used in subsection (j)) that--

(A) has been approved under subsection (c); and

(B) is marketed, sold, or distributed directly or indirectly to retail class of trade under a different labeling, packaging (other than repackaging as the listed drug in blister packs, unit doses, or similar packaging for use in institutions), product code, labeler code, trade name, or trade mark than the listed drug.

(u) Certain drugs containing single enantiomers

(1) In general

For purposes of subsections (c)(3)(E)(ii) and (j)(5)(F)(ii), if an application is submitted under subsection (b) for a non-racemic drug containing as an active ingredient (including any ester or salt of the active ingredient) a single enantiomer that is contained in a racemic drug approved in another application under subsection (b), the applicant may, in the application for such non-racemic drug, elect to have the single enantiomer not be considered the same active ingredient as that contained in the approved racemic drug, if--

(A)(i) the single enantiomer has not been previously approved except in the approved racemic drug; and

(ii) the application submitted under subsection (b) for such non-racemic drug--

(I) includes full reports of new clinical investigations (other than bioavailability studies)--

(aa) necessary for the approval of the application under subsections (c) and (d); and

(bb) conducted or sponsored by the applicant; and

(II) does not rely on any clinical investigations that are part of an application submitted under subsection (b) for approval of the approved racemic drug; and

(B) the application submitted under subsection (b) for such non-racemic drug is not submitted for approval of a condition of use--

(i) in a therapeutic category in which the approved racemic drug has been approved; or

(ii) for which any other enantiomer of the racemic drug has been approved.

(2) Limitation

(A) No approval in certain therapeutic categories

Until the date that is 10 years after the date of approval of a non-racemic drug described in paragraph (1) and with respect to which the applicant has made the election provided for by such paragraph, the Secretary shall not approve such non-racemic drug for any condition of use in the therapeutic category in which the racemic drug has been approved.

(B) Labeling

If applicable, the labeling of a non-racemic drug described in paragraph (1) and with respect to which the applicant has made the election provided for by such paragraph shall include a statement that the non-racemic drug is not approved, and has not been shown to be safe and effective, for any condition of use of the racemic drug.

(3) Definition

(A) In general

For purposes of this subsection, the term "therapeutic category" means a therapeutic category identified in the list developed by the United States Pharmacopeia pursuant to section 1395w-104(b)(3)(C)(ii) of Title 42 and as in effect on September 27, 2007.

(B) Publication by Secretary

The Secretary shall publish the list described in subparagraph (A) and may amend such list by regulation.

(4) Availability

The election referred to in paragraph (1) may be made only in an application that is submitted to the Secretary after September 27, 2007, and before October 1, 2017.

(v) Antibiotic drugs submitted before November 21, 1997

(1) Antibiotic drugs approved before November 21, 1997

(A) In general

Notwithstanding any provision of the Food and Drug Administration Modernization Act of 1997 or any other provision of law, a sponsor of a drug that is the subject of an application described in subparagraph (B)(i) shall be eligible for, with respect to the drug, the 3-year exclusivity period referred to under clauses (iii) and (iv) of subsection (c)(3)(E) and under clauses (iii) and (iv) of subsection (j)(5)(F), subject to the requirements of such clauses, as applicable.

(B) Application; antibiotic drug described

(i) Application

An application described in this clause is an application for marketing submitted under this section after October 8, 2008 in which the drug that is the subject of the application contains an antibiotic drug described in clause (ii).

(ii) Antibiotic drug

An antibiotic drug described in this clause is an antibiotic drug that was the subject of an application approved by the Secretary under section 357 of this title (as in effect before November 21, 1997).

(2) Antibiotic drugs submitted before November 21, 1997, but not approved

(A) In general

Notwithstanding any provision of the Food and Drug Administration Modernization Act of 1997 or any other provision of law, a sponsor of a drug that is the subject of an application described in subparagraph (B)(i) may elect to be eligible for, with respect to the drug--

(i)(I) the 3-year exclusivity period referred to under clauses (iii) and (iv) of subsection (c)(3)(E) and under clauses (iii) and (iv) of subsection (j)(5)(F), subject to the requirements of such clauses, as applicable; and

(II) the 5-year exclusivity period referred to under clause (ii) of subsection (c)(3)(E) and under clause (ii) of subsection (j)(5)(F), subject to the requirements of such clauses, as applicable; or

(ii) a patent term extension under section 156 of Title 35 subject to the requirements of such section.

(B) Application; antibiotic drug described

(i) Application

An application described in this clause is an application for marketing submitted under this section after October 8, 2008 in which the drug that is the subject of the application contains an antibiotic drug described in clause (ii).

(ii) Antibiotic drug

An antibiotic drug described in this clause is an antibiotic drug that was the subject of 1 or more applications received by the Secretary under section 357 of this title (as in effect before November 21, 1997), none of which was approved by the Secretary under such section.

(3) Limitations

(A) Exclusivities and extensions

Paragraphs (1)(A) and (2)(A) shall not be construed to entitle a drug that is the subject of an approved application described in subparagraphs [5] (1)(B)(i) or (2)(B)(i), as applicable, to any market exclusivities or patent extensions other than those exclusivities or extensions described in paragraph (1)(A) or (2)(A).

(B) Conditions of use

Paragraphs (1)(A) and (2)(A)(i) shall not apply to any condition of use for which the drug referred to in subparagraph (1)(B)(i) or (2)(B)(i), as applicable, was approved before October 8, 2008.

(4) Application of certain provisions

Notwithstanding section 125, or any other provision, of the Food and Drug Administration Modernization Act of 1997, or any other provision of law, and subject to the limitations in paragraphs (1), (2), and (3), the provisions of the Drug Price Competition and Patent Term Restoration Act of 1984 shall apply to any drug subject to paragraph (1) or any drug with respect to which an election is made under paragraph (2)(A).

(w) Deadline for determination on certain petitions

The Secretary shall issue a final, substantive determination on a petition submitted pursuant to subsection (b) of section 314.161 of title 21, Code of Federal Regulations (or any successor regulations), no later than 270 days after the date the petition is submitted.

(x) Date of approval in the case of recommended controls under the CSA

(1) In general

In the case of an application under subsection (b) with respect to a drug for which the Secretary provides notice to the sponsor that the Secretary intends to issue a scientific and medical evaluation and recommend controls under the Controlled Substances Act, approval of such application shall not take effect until the interim final rule controlling the drug is issued in accordance with section 201(j) of the Controlled Substances Act.

(2) Date of approval

For purposes of this section, with respect to an application described in paragraph (1), the term "date of approval" shall mean the later of--

(A) the date an application under subsection (b) is approved under subsection (c); or

(B) the date of issuance of the interim final rule controlling the drug.

CREDIT(S)

(June 25, 1938, c. 675, § 505, 52 Stat. 1052; 1940 Reorg. Plan No. IV, § 12, eff. June 30, 1940, 5 F.R. 2422, 54 Stat. 1237; June 25, 1948, c. 646, § 32(b), 62 Stat. 991; May 24, 1949, c. 139, § 127, 63 Stat. 107; 1953 Reorg. Plan No. 1, § 5, eff. Apr.

11, 1953, 18 F.R. 2053, 67 Stat. 631; Pub.L. 86-507, § 1(18), June 11, 1960, 74 Stat. 201; Pub.L. 87-781, Title I, §§ 102(b) to (d), 103(a), (b), 104(a) to (d)(2), Oct. 10, 1962, 76 Stat. 781-783, 784, 785; Pub.L. 92-387, § 4(d), Aug. 16, 1972, 86 Stat. 562; Pub.L. 98-417, Title I, §§ 101, 102(a) to (b)(5), 103, 104, Sept. 24, 1984, 98 Stat. 1585, 1592, 1593, 1597; Pub.L. 102-282, § 5, May 13, 1992, 106 Stat. 161; Pub.L. 103-80, § 3(n), Aug. 13, 1993, 107 Stat. 777; Pub.L. 105-115, Title I, §§ 115(a), (b), 117, 119, 120, 124(a), Nov. 21, 1997, 111 Stat. 2313, 2315, 2316, 2318, 2324; Pub.L. 106-113, Div. B, § 1000(a)(9) [Title IV, § 4732(b)(11)], Nov. 29, 1999, 113 Stat. 1536, 1501A-584; Pub.L. 107-109, § 15(c)(1), Jan. 4, 2002, 115 Stat. 1420; Pub.L. 108-155, § 2(b)(1), Dec. 3, 2003, 117 Stat. 1941; Pub.L. 108-173, Title XI, §§ 1101(a), (b), 1102(a), 1103(a), Dec. 8, 2003, 117 Stat. 2448, 2452, 2457, 2460; Pub.L. 110-85, Title VII, § 701(b), Title VIII, § 801(b)(3)(A), (B), Title IX, §§ 901(a), 903, 905(a), 914(a), 915, 916, 918, 920, 921, Title XI, § 1113, Sept. 27, 2007, 121 Stat. 903, 921, 922, 943, 944, 953, 957 to 962, 976; Pub.L. 110-316, Title III, § 301, Aug. 14, 2008, 122 Stat. 3524; Pub.L. 110-379, § 4(a), Oct. 8, 2008, 122 Stat. 4076; Pub.L. 111-31, Div. A, Title I, § 103(e), June 22, 2009, 123 Stat. 1837; Pub.L. 111-148, Title VII, § 7002(d)(1), Title X, § 10609, Mar. 23, 2010, 124 Stat. 816, 1014; Pub.L. 112-144, Title IX, § 905, Title XI, §§ 1101, 1134(a), 1135, July 9, 2012, 126 Stat. 1092, 1108, 1123; Pub.L. 113-5, Title III, § 301, Mar. 13, 2013, 127 Stat. 179; Pub.L. 114-89, § 2(a)(1), Nov. 25, 2015, 129 Stat. 698.)

Footnotes

1 So in original. Probably should be “bioavailability”.

2 So in original. Probably should be “drug,”.

3 So in original. Probably should be preceded by “the”.

4 So in original. Probably should be “years”.

5 So in original. Probably should be “subparagraph”.

21 U.S.C.A. § 355, 21 USCA § 355

Current through P.L. 114-143. Also includes P.L. 114-145, 114-146, and 114-148.

End of Document

EXHIBIT “D”

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

18-972

Approval Letter(s)

DEC 24 1985

NDA 18-972

Sanofi Pharmaceuticals, Inc.
c/o Ives Laboratories Inc.
Attention: Robert H. Harris, Ph.D.
685 Third Avenue
New York, NY 10017

Dear Dr. Harris:

Please refer to your March 14, 1983 new drug application resubmitted on June 28, 1983 and April 4, 1984 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Cordarone (amiodarone HCl) Tablets.

We also acknowledge receipt of your amendments dated May 6 and 10, 1983; June 28, 1983; August 31, 1983; September 1 (two), and 16, 1983; January 9, 17, 24 and 27, 1984; February 9 and 28, 1984; March 28, 1984; April 2, 6, 27 and 30, 1984; May 25, 1984 (two); June 12, 1984; July 31, 1984; August 17 and 22, 1984; September 19, 1984; October 4, 1984; November 2 and 13 (two), 1984; December 18, 1984; February 11, 1985; May 3, 10 and 17, 1985; an undated letter we received on October 23, 1985; and December 23, 1985.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted draft labeling. Accordingly, the application is approved. Prior to marketing, however, please submit twelve copies of the final printed labeling that are identical to the enclosed draft. Please individually mount seven copies of the labeling on heavy weight paper or similar material.

We also recommend that repeat teratology (Segment II) studies be conducted with amiodarone in two species according to FDA Guidelines for Reproduction Studies in order to be in a position to defend broadening of indications. For the population currently indicated, such studies are not required.

It is also our understanding that you have agreed to pursue the following diligently:

1. The Mason survey. The survey initiated by Jay Mason and members of his group constitutes a data base that, given the individuals involved, is of potentially very high quality; it reflects a larger long term experience than is otherwise available in detail. Its analysis should be completed. I have spoken to Dr. Mason, who assures me that he is eager to work with Ives to complete the analysis and evaluation of these data. He would make the raw data (the responses to the survey) available to Ives so that they can carry out their own analysis. I believe that these and other arrangements can be worked out readily if there is a desire to do so and I would be happy to serve as a "broker" between the two parties.

2. There are a number of groups carrying out detailed evaluations of pulmonary function and pulmonary toxicity in patients receiving amiodarone. Preliminary reports that appeared in the most recent American Heart Association meeting suggest, at least the possibility, that monitoring of diffusion capacity may give early warning of patients at risk for serious pulmonary disease, perhaps allowing dosage adjustment or even trials of therapy, such as corticosteroids. It is important to attempt to get the underlying data from these studies and evaluate them.

3. We expect you to continue to review regularly all published clinical literature on amiodarone, as well as any other data of interest, so that the labeling can be modified and updated as needed. We would expect to see a review of new literature approximately quarterly with recommendations for labeling revision as needed.

4. Approved labeling does not allow claims related to atrial arrhythmias but the potential usefulness of amiodarone in these arrhythmias is widely recognized. Controlled clinical trials in patients with atrial arrhythmias need to be conducted.

The objectives of such trials would include dose-response, efficacy and safety, with an emphasis on defining the range of useful doses in at least the different classes of atrial arrhythmias. Development of such a program will require careful thought. Consult with the Division of Cardio-Renal Drug Products as often as you wish during your efforts in designing the program.

5. It will almost certainly prove difficult to carry out randomized controlled trials in patients with life threatening arrhythmias, but there are populations in whom randomized trials are reasonable and the outcomes potentially very important. High risk post infarction patients (patients with relatively frequent ventricular premature beats and low ejection fractions) would be highly suitable candidates for a clinical trial and have no present identified effective therapy. It should be possible and desirable to carry out a trial of amiodarone vs placebo in these patients. An alternative would be to compare amiodarone to individualized alternative therapy, although the possibility that these treatments are actually detrimental must be explored; CAPS results may prove helpful in this. We are eager to discuss the kinds of trials that might be carried out at your earliest convenience.

6. The effects of amiodarone on thyroid function and TSH levels in man are not completely defined at present. Clarification and a change in labeling to include new information is also expected at your earliest convenience.

We would appreciate your submitting copies of the introductory promotional material that you propose to use for this product. Please submit one copy to the Division of Cardio-Renal Drug Products and a second copy, along with the package insert, directly to the Director, Division of Drug Advertising and Labeling (HFN-240). Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

We understand that you have agreed not to advertise or market this product until your advertising material and promotional plan have been reviewed by the Division of Drug Advertising and the Office of Drug Research and Review and have been approved.

Please submit one market package of the drug when available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Cathy Heald
Consumer Safety Officer
(301) 443-4730

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
~~Original NDA~~
HFN-110
HFN-110/CSO
HFN-83
HFN-240 (with labeling)
HFN-100/Dr. Temple
HFN-232 (with labeling)
HFN-110/CHeald/12/18/85;12/18/85/12/23/85
sb/12/18/85;12/20/85/2559s
klb/12-20-85;sh/12/23/85
R/D: RLipicky/12/19/85/12/20/85
MCommarato/12/20/85
CResnick/12/20/85
PLMartese/12/20/85
CHeald/12/20/85
RWolters/12/20/85
NMorgenstern/12/20/85

12/23/85

12/23/85

RR 12/23/85

APPROVAL 12/24/85

12-24-85

CHeald 12 23-85

EXHIBIT “E”

[Code of Federal Regulations]
[Title 21, Volume 4]
[Revised as of April 1, 2015]
[CITE: 21CFR201.56]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER C--DRUGS: GENERAL

PART 201 -- LABELING

Subpart B--Labeling Requirements for Prescription Drugs and/or Insulin

Sec. 201.56 Requirements on content and format of labeling for human prescription drug and biological products.

(a) *General requirements.* Prescription drug labeling described in 201.100(d) must meet the following general requirements:

(1) The labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug.

(2) The labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular. In accordance with 314.70 and 601.12 of this chapter, the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.

(3) The labeling must be based whenever possible on data derived from human experience. No implied claims or suggestions of drug use may be made if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness. Conclusions based on animal data but necessary for safe and effective use of the drug in humans must be identified as such and included with human data in the appropriate section of the labeling.

(b) *Categories of prescription drugs subject to the labeling content and format requirements in 201.56(d) and 201.57.* (1) The following categories of prescription drug products are subject to the labeling requirements in paragraph (d) of this section and 201.57 in accordance with the implementation schedule in paragraph (c) of this section:

(i) Prescription drug products for which a new drug application (NDA), biologics license application (BLA), or efficacy supplement was approved by the Food and Drug Administration (FDA) between June 30, 2001 and June 30, 2006;

(ii) Prescription drug products for which an NDA, BLA, or efficacy supplement is pending on June 30, 2006; or

(iii) Prescription drug products for which an NDA, BLA, or efficacy supplement is submitted anytime on or after June 30, 2006.

(2) Prescription drug products not described in paragraph (b)(1) of this section are subject to the labeling requirements in paragraph (e) of this section and 201.80.

(c) *Schedule for implementing the labeling content and format requirements in 201.56(d) and 201.57.* For products described in paragraph (b)(1) of this section, labeling conforming to the requirements in paragraph (d) of this

section and 201.57 must be submitted according to the following schedule:

(1) For products for which an NDA, BLA, or efficacy supplement is submitted for approval on or after June 30, 2006, proposed conforming labeling must be submitted as part of the application.

(2) For products for which an NDA, BLA, or efficacy supplement is pending on June 30, 2006, or that has been approved any time from June 30, 2005, up to and including June 30, 2006, a supplement with proposed conforming labeling must be submitted no later than June 30, 2009.

(3) For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2004, up to and including June 29, 2005, a supplement with proposed conforming labeling must be submitted no later than June 30, 2010.

(4) For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2003, up to and including June 29, 2004, a supplement with proposed conforming labeling must be submitted no later than June 30, 2011.

(5) For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2002, up to and including June 29, 2003, a supplement with proposed conforming labeling must be submitted no later than June 30, 2012.

(6) For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2001, up to and including June 29, 2002, a supplement with proposed conforming labeling must be submitted no later than June 30, 2013.

(d) *Labeling requirements for new and more recently approved prescription drug products.* This paragraph applies only to prescription drug products described in paragraph (b)(1) of this section and must be implemented according to the schedule specified in paragraph (c) of this section.

(1) Prescription drug labeling described in 201.100(d) must contain the specific information required under 201.57(a), (b), and (c) under the following headings and subheadings and in the following order:

Highlights of Prescribing Information

Product Names, Other Required Information

Boxed Warning

Recent Major Changes

Indications and Usage

Dosage and Administration

Dosage Forms and Strengths

Contraindications

Warnings and Precautions

Adverse Reactions

Drug Interactions

Use in Specific Populations

Full Prescribing Information: Contents

Full Prescribing Information

Boxed Warning

1 Indications and Usage

2 Dosage and Administration

3 Dosage Forms and Strengths

4 Contraindications

5 Warnings and Precautions

6 Adverse Reactions

7 Drug Interactions

8 Use in Specific Populations

8.1 Pregnancy

8.2 Lactation

8.3 Females and Males of Reproductive Potential

8.4 Pediatric use

8.5 Geriatric use

9 Drug Abuse and Dependence

9.1 Controlled substance

9.2 Abuse

9.3 Dependence

10 Overdosage

11 Description

12 Clinical Pharmacology

12.1 Mechanism of action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 Nonclinical Toxicology

13.1 Carcinogenesis, mutagenesis, impairment of fertility

13.2 Animal toxicology and/or pharmacology

14 Clinical Studies

15 References

16 How Supplied/Storage and Handling

17 Patient Counseling Information

(2) Additional nonstandard subheadings that are used to enhance labeling organization, presentation, or ease of use (e.g., for individual warnings or precautions, or for each drug interaction) must be assigned a decimal number that corresponds to their placement in labeling. The decimal numbers must be consistent with the standardized identifying numbers listed in paragraph (d)(1) of this section (e.g., subheadings added to the "Warnings and Precautions" section must be numbered 5.1, 5.2, and so on).

(3) Any reference in Highlights to information appearing in the full prescribing information must be accompanied by the identifying number (in parentheses) corresponding to the location of the information in the full prescribing information.

(4) Omit clearly inapplicable sections, subsections, or specific information. If sections or subsections required under paragraph (d)(1) of this section are omitted from the full prescribing information, the heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of Contents: "* Sections or subsections omitted from the full prescribing information are not listed."

(5) Any risk information that is required under 201.57(c)(9)(iv) is considered "appropriate pediatric contraindications, warnings, or precautions" within the meaning of section 505A(l)(2) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355A(l)(2)), whether such information appears in the "Contraindications," "Warnings and Precautions," or "Use in Specific Populations" section of labeling.

(e) *Labeling requirements for older prescription drug products.* This paragraph applies only to approved prescription drug products not described in paragraph (b)(1) of this section.

(1) Prescription drug labeling described in 201.100(d) must contain the specific information required under 201.80 under the following section headings and in the following order:

Description

Clinical Pharmacology

Indications and Usage

Contraindications

Warnings

Precautions

Adverse Reactions

Drug Abuse and Dependence

Overdosage

Dosage and Administration

How Supplied

(2) The labeling may contain the following additional section headings if appropriate and if in compliance with 201.80(l) and (m):

Animal Pharmacology and/or Animal Toxicology

Clinical Studies

References

(3) Omit clearly inapplicable sections, subsections, or specific information.

(4) The labeling may contain a "Product Title" section preceding the "Description" section and containing only the information required by 201.80 (a)(1)(i), (a)(1)(ii), (a)(1)(iii), and (a)(1)(iv) and 201.100(e). The information required by 201.80(a)(1)(i) through (a)(1)(iv) must appear in the "Description" section of the labeling, whether or not it also appears in a "Product Title."

(5) The labeling must contain the date of the most recent revision of the labeling, identified as such, placed prominently immediately after the last section of the labeling.

(6) The requirement in 201.80(f)(2) to reprint any FDA-approved patient labeling at the end of prescription drug labeling or accompany the prescription drug labeling must be implemented no later than June 30, 2007.

[71 FR 3986, Jan. 24, 2006, as amended at 79 FR 72101, Dec. 4, 2014]

EXHIBIT “F”

POLITICS & GOVERNMENT NOVEMBER 4, 2003 6:24 PM

FDA oversight of 'off-label' drug use wanes as prescriptions rise

HIGHLIGHTS

Millions of patients are being given drugs by their doctors that the FDA hasn't approved for treating their particular illnesses. Off-label prescribing, as it's called, puts patients at risk while offering no assurance the drugs will work.

Martha Andreasen, of Bowie, Texas, with her husband, Terry, lives with badly damaged lungs after taking the drug Pacerone. The drug, also called amiodarone, wasn't FDA-approved for her heart condition. Joyce Marshall / Fort Worth Star-Telegram / MCT

Chris Adams and Alison Young - McClatchy Newspapers

WASHINGTON — In 1962, a Congress horrified that thousands of European babies had been deformed by the medication thalidomide ordered the Food and Drug Administration to make sure the same thing never happened in America.

Congress gave the FDA the power to assess the safety and effectiveness of all drugs before they could be sold on the U.S. market.

Forty years later, however, an ever-growing segment of the American pharmaceutical business is eluding that rigorous scrutiny. Millions of patients are being given drugs by their doctors that the FDA hasn't approved for treating their particular illnesses. Off-label prescribing, as it's called, puts patients at risk while offering no assurance the drugs will work.

And while the FDA has argued in court that the "risk to the public from unproven uses of drugs and devices is both real and substantial," the agency rarely has tried to curb it. When it attempted to do so in the 1990s, its efforts fizzled.

Now as the phenomenon soars — Knight Ridder found that off-label prescribing for a sample of top-selling drugs has nearly doubled in the last five years — the Bush administration has opened the door to doing even less to stop it.

Saying recent court rulings have eroded its power, the FDA has sought public comment on whether drug makers should have more leeway to market the unapproved uses of their profitable drugs. Overseeing the effort is a Bush appointee who, before coming to the FDA, helped sue the agency over its marketing and advertising restrictions.

"They certainly are backing off," said Michael Wilkes, the vice dean at the School of Medicine at the University of California, Davis. He studied off-label promotions for the FDA in the 1990s.

In part, the agency is handcuffed by a conflicted mandate from Congress. The FDA is trying to do many things: Get powerful drugs to market while protecting the public, respect the First Amendment while regulating drug advertising and let doctors practice as they see fit — except when they make dumb errors. Given the rapidly growing number of drugs in the marketplace, prescribing is far more complicated for doctors today.

"There's some limit to what the federal government should do, I think, because it's not going to be effective," said Dr. Janet Woodcock, the director of the FDA's drug division. "You can't just Band-Aid and patch something that has systemic, underlying problems."

But it's also clear that the agency hasn't followed through on its limited efforts to reduce the risks of off-label drug sales:

- Under FDA rules, if a drug maker knows a drug is being used for off-label purposes, it's required to come forward with evidence supporting those unapproved uses. FDA officials said in a court deposition that the rule had not been enforced.
- After the FDA took a major drug company to court in 1993 and won a hefty payment for overt off-label sales pitches, its commissioner vowed to use such sanctions again to control illicit marketing. But FDA officials could point to no other case since then when they have.
- Last year, the FDA issued 28 violation letters for improper drug marketing, down from 158 in 1998. The agency said it would need nearly twice as many people to adequately police the industry's 37,000 advertisements and other promotions each year.
- Twenty-four years ago, the FDA said it wanted to ensure that patients got useful, easy-to-understand information about the drugs they took. Most still don't.

The bottom line for consumers: Beware.

"We as patients have got to raise the questions ourselves and take care of our own selves," said Jere Goyan, who was FDA commissioner from 1979 to 1981.

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The drug Kristen Pettijohn took was called Avelox. It's part of a family of antibiotics called fluoroquinolones.

Those powerful but risky drugs are intended for patients who are fighting particular bacterial bugs. But they're widely prescribed off-label for less serious illnesses, sometimes even to treat viruses, which can't be killed by antibiotics.

A study this year funded by the National Institutes of Health reviewed 100 emergency room prescriptions for fluoroquinolones and found that only 19 were written for appropriate conditions and only one was given in the correct dose and for the proper duration.

The FDA long has been aware of the possibility that Avelox could be misused.

Just before it approved Avelox in 1999, a member of the agency's expert review panel — Robert Danner, a critical care expert at the NIH _ offered a warning: "This is exactly the kind of place that you get into trouble. I am absolutely convinced that the drug will be used differently once it's marketed frequently."

Avelox was approved, however, and marketed hard by Bayer Corp. In 1999 and 2001, the FDA admonished company officials for encouraging unapproved uses.

This past May, Pettijohn, a gregarious 23-year-old nursing student from Batesville, Ind., who recently had gotten engaged, picked up the persistent cold that had been running through her family. "Her version was a little worse than ours," said her father, Gary Pettijohn. "I would say it was moderate at best."

Early in the morning of May 15, Pettijohn's mother took her to an emergency room. Going there, Pettijohn told her mom, would be quicker than waiting for an appointment with their family physician.

Forty-two minutes later, Pettijohn was on her way to the drugstore. The doctor had diagnosed her with acute bronchitis and prescribed Avelox. The potent antibiotic's label says it's approved for cases of chronic, or long-term, bronchitis, and only after blood tests have been taken to identify the bacteria causing the problem. Her medical records show no blood work was done.

That was a Thursday. By Sunday, Pettijohn was nauseated and suffering abdominal pain. Her mother packed a plastic bag with the remaining Avelox pills and took her to the hospital.

Over the next five days, Pettijohn was incoherent. She had a burning rash and her skin began peeling off. She slipped into a coma, resting on an air bed, totally wrapped as though she were a severe burn patient.

By Wednesday, a doctor approached Gary and Ruth Pettijohn.

"Our problem just got twice as difficult," he said. "She has two life-threatening conditions simultaneously."

Pettijohn's liver was in full failure, and she was experiencing a form of Stevens-Johnson syndrome, a rare and extreme drug reaction mentioned on the Avelox label.

She had a liver transplant on Friday. The doctors reported that her old liver had turned to mush and fallen apart in their hands.

Soon after the operation, Pettijohn had a heart attack, then another. Her death certificate cited Avelox as the prime contributing factor in her death.

The hospital had no comment about her death. Bayer had no comment beyond saying the death "was promptly and accurately reported to the FDA," and that it thinks its antibiotic should be prescribed only for approved conditions.

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As Congress reworked the nation's drug-safety laws after thalidomide, it sought to create a regulatory system that guaranteed that the drugs Americans used were safe and effective.

Lawmakers in 1962 worried that drug makers might be tempted to get a medication approved for one use and then promote it for others. "The initial claim would tend to be quite limited," said a group of senators led by the late Tennessee Democrat Estes Kefauver. "Thereafter, the sky would be the limit. Extreme claims of any kind could be made."

Congress told the FDA to require stringent tests before a drug could get to market. Once a drug passed, a company could advertise it only for the approved uses.

The FDA began reviewing all the drugs that had been on the market as of 1962, when the new approval rules kicked in. Of 3,443 drugs commonly prescribed, 1,124, or one-third, were deemed useless and taken off the market, FDA records show.

Even though that shows that doctors often can't judge drugs' effectiveness, the FDA largely has stayed out of the doctor's office.

The agency's rules say it can require a drug company to prove that an off-label use is safe and effective. The FDA has said that a drug's "actual use" by doctors can show a drug maker's "intent" in selling it.

However, asked in a lawsuit deposition in 1996 if the FDA had ever considered using the option of requiring proof of off-label effectiveness, the agency's Dr. Robert Temple replied: "We think about this all the time. We just don't know quite how to do it."

Knight Ridder found that the off-label use for some drugs is as high as 90 percent of all prescriptions sold for it.

Off-label uses became a concern in the 1990s, under the activist tenure of then-Commissioner David A. Kessler, who noted that "medical history is replete with examples of products and procedures that were based on medical anecdote, not evidence, and were thought for years by most clinicians to be effective, but later turned out to be useless and sometimes even dangerous."

In 1991, the FDA established a task force to examine off-label uses of drugs and medical devices.

The agency also found that drug companies often had no incentive to evaluate the merits of off-label prescribing because they might discover that their drugs didn't work when prescribed off-label and sales would suffer, according to a review of FDA records.

The drug makers, which are among the most profitable industries in the United States, know they can continue to get off-label sales without going through the expense of proving a drug's effectiveness for the off-label use to the FDA.

Also interfering is the patent protection process. Once a drug's patent lapses, there's little financial interest in taking on the added costs of new FDA application.

Based in part on the work of the off-label task force, the FDA attempted a host of fixes. But a decade later, those efforts largely have fallen short:

- One push was to have companies apply for FDA approval for popular off-label treatments. While the effort initially produced more applications, the numbers have been dropping. From 1998 to 2002, the number of approvals for new uses of existing drugs went from 74 to 39, according to the FDA.

- An attempt to revise the prescribing labels for doctors has dragged on for more than 10 years. The agency says its labels are confusing even for doctors, and that fixing them could reduce medication errors.
- Proposals to give patients more meaningful drug information have been stalled even longer. The FDA repeatedly backed away from plans, dating to 1979, to ensure that all patients get basic information about the drugs they buy. Opposition has been fierce. Doctors have argued that the information would frighten patients unnecessarily. Today, most of the leaflets patients get about drugs are part of an industry-run voluntary program. The quality of the information they provide varies widely, with only about half of the leaflets studied meeting FDA goals for usefulness, according to an FDA-commissioned study announced last year.
- Proposals to restrict drug makers' efforts to get around the ban on promoting off-label drug uses ran into a blizzard of legal challenges by the Washington Legal Foundation, a free-market advocacy group. On free-speech grounds, the courts turned away many of the FDA's arguments; U.S. District Judge Royce Lamberth said the "FDA exaggerates its overall place in the universe."

Helping the Washington Legal Foundation make its case was Daniel Troy, a prominent First Amendment and corporate lawyer. Today, Troy is chief counsel of the FDA, a Bush administration appointee who has started a process that could substantially rewrite the FDA's rules on commercial speech, including those regulating off-label drug promotions.

The pharmaceutical industry has jumped on the opportunity, pushing the agency to relax some of its restrictions on promoting off-label uses. Consumer groups, such as Public Citizen Health Research Group, and many congressional Democrats say to do so would invite disaster.

FDA Commissioner Mark B. McClellan, a physician, said the agency would like to see more evidence submitted about off-label uses, stressing that it was important for such treatments to meet the "gold standard" of FDA approval.

To help curb risky off-label prescribing, he wants to improve the FDA's system for reporting drugs' side effects, and he wants better information in the hands of doctors and consumers. The effort to rewrite the labels doctors read will be finished "in a matter of months," he said. "I think we can do much better than we have."

The FDA has had some success using its authority to get the pharmaceutical industry to study drugs' affects on children and put that information on the label. Those efforts, begun in the 1990s and involving congressional and agency action, have produced some results, although they recently have been set back in court.

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In many ways, the FDA's 1962 mandate to determine whether drugs are safe and effective is irrelevant in today's market, in which some off-label treatments have become so widespread that they're now considered the standard of care.

Amiodarone — under the brand name Pacerone — was the drug taken by George Cox, a Buckner, Mo., man who lost nearly all his sight, and by Martha Andreasen of Bowie, Texas, who's struggling with lung damage.

Amiodarone can have a devastating effect on the lungs: As many as 17 percent of patients in some studies experienced lung damage, and about 10 percent of them died. Patients taking the drug have suffered thyroid, liver and eye problems, including blindness. The FDA approved it only as a drug of last resort for patients with a life-threatening heart condition called ventricular tachycardia.

In 1999, Cox, now 75, was given amiodarone for atrial flutter, a heart condition that isn't life-threatening. He got the prescription a full decade after the FDA began telling the drug's makers to stop promoting it as something other than a last-resort drug.

Andreasen also was given amiodarone off-label. She had atrial fibrillation, a common heart problem similar to atrial flutter. Like many patients, she said she was never warned of the drug's risks or that her prescription was off-label. Her pharmacy leaflet mentioned nausea and dizziness, but not death from lung problems.

Today, Andreasen is tethered to an oxygen tank each night, and at age 54 she's already made her funeral arrangements. She's homebound and doesn't have the strength to clean her house, a humiliating letdown for a woman who's been a member of her town's Young Homemakers club for 30 years. Since she was dropped by her husband's health insurance, the Andreasens now pay $800 a month for high-risk insurance and co-payments. Their dining room table sits atop plywood because they can't afford to finish a repair to the floor.

"The FDA is supposed to protect the general public from situations such as this _ or so I thought," Andreasen said.

Since at least 1988, the FDA has warned two drug companies to stop false and misleading promotions that downplayed amiodarone's risks while suggesting it as a first-line therapy. The agency sent letters to amiodarone makers in 1989, 1992 and 1998. "Your firm has an intolerable record of compliance with the law," read the 1989 letter to Wyeth, one of the amiodarone makers.

Wyeth's promotions continued. From 1999 to 2002, a slick magazine-style brochure that Wyeth paid for proclaimed "Amiodarone From Last to First-Line Antiarrhythmic Therapy" on its glossy purple cover.

Wyeth spokesman Doug Petkus said the brochure was educational, not promotional. Regardless, Wyeth no longer is doing any promotion of its amiodarone drug, Cordarone, because its patent protection has expired.

After Cox lost most of his sight, his Missouri pharmacist gave him Wyeth's "First-Line" brochure, and he passed it on to the FDA in 2001.

The agency wrote back, saying it can "take action when unapproved (off-label) uses become widespread or endanger the public health," but until last month it had done little to try to curb the widespread off-label prescribing of amiodarone.

In the last year, doctors wrote nearly 2.3 million off-label amiodarone prescriptions, according to Knight Ridder's analysis. That's 82 percent of all the prescriptions for the drug.

In response to Knight Ridder's findings, the FDA's Woodcock said the agency would require that all amiodarone prescriptions be accompanied by an FDA-approved patient guide to ensure that consumers know exactly what the drug is approved for and what its dangers are. Patients will get the guides starting early next year.

"What you brought to the table was the extent of off-label use and some specific patient experiences of not getting all of the information about this drug," Woodcock said.

"Obviously this drug is a very risky drug," she said.

While many cardiologists defend amiodarone's off-label use for atrial fibrillation, a recent NIH study challenged their long-held beliefs.

Called AFFIRM, the study concluded that patients taking drugs such as amiodarone to control their hearts' rhythm experienced more side effects and hospitalizations than those given safer drugs to control how fast their hearts beat. For all its extra risks, amiodarone was no more effective.

Dr. Claude Lenfant, the recently retired director of NIH's National Heart, Lung and Blood Institute, said amiodarone didn't appear to be the best treatment for many patients with atrial fibrillation. But changing a doctor's practice "takes place very, very slowly."

"I personally feel there's a system failure," he said.

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Even when it's aggressive, the FDA has been unable to stem off-label prescribing.

For more than a decade, the FDA has tried to corral the use of Accutane — a drug for severe forms of acne — which can cause birth defects.

As early as 1990, a frustrated FDA official wrote that "intensive regulation has not, cannot and will not achieve the Agency's goal of eliminating pregnancy exposure to Accutane." At the time, the official estimated that 90 percent of Accutane's use by women was off-label, typically for mild acne that can be treated with safer drugs.

Even tough new warnings on the drug's label about suicide, psychosis and depression didn't stop sales.

According to an internal company sales plan for 2001, drug maker Roche concluded that despite extensive media coverage about those new dangers, "prescribers were apparently unmoved by this information."

In 2002, the same FDA official made another estimate that 90 percent of Accutane use was off-label. The company disputes the FDA estimate. __

Thalidomide's entry into the U.S. market shows how physicians and the drug industry consider the FDA irrelevant.

The drug was approved in 1998 for a leprosy-related skin condition that's virtually nonexistent in the United States.

After studies showed that the drug might be useful for treating multiple myeloma, a form of cancer, Celgene Corp. aggressively sold that idea to doctors.

One company sales representative went further, telling an oncologist that the drug, marketed as Thalomid, is "good for weight loss," could be used "as an appetite stimulant" and is a "great drug for feelings of general well-being," according to an FDA document describing the sales pitch.

When the doctor asked whether the FDA had approved Thalomid for those uses, the sales rep said, "No, but do you want some material anyway?"

In 2002, the FDA told Celgene that its existing data on multiple myeloma wouldn't be enough to win the agency's approval. The earliest the company says it might seek authorization as a treatment for that form of cancer is 2005.

Today, 70 percent of Thalomid uses are for multiple myeloma, while only 1 percent are for its approved leprosy condition. Celgene, in filings with the Securities and Exchange Commission, declared: "We may not be able to attain or maintain profitability" if physicians prescribe Thalomid only for patients who are diagnosed with leprosy. __

(Researcher Tish Wells contributed to this report.)

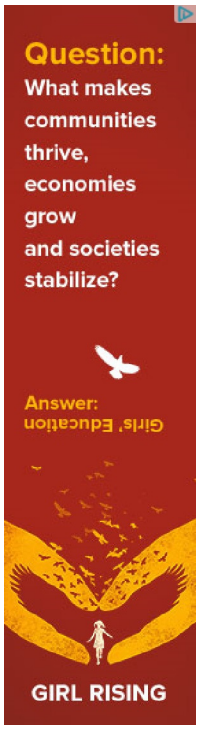

EXHIBIT “G”

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Medication Guides

Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm) and DailyMed (http://dailymed.nlm.nih.gov/dailymed/about.cfm) also contain medication guides as part of drug labeling.

Get email alerts when the Medication Guides page is updated. (https://public.govdelivery.com/accounts/USFDA/subscriber/new?topic_id=USFDA_224)

Medication Guides are paper handouts that come with many prescription medicines. The guides address issues that are specific to particular drugs and drug classes, and they contain FDA-approved information that can help patients avoid serious adverse events.

FDA requires that Medication Guides be issued with certain prescribed drugs and biological products when the Agency determines that:

- certain information is necessary to prevent serious adverse effects
- patient decision-making should be informed by information about a known serious side effect with a product, or
- patient adherence to directions for the use of a product are essential to its effectiveness.

Please note: All links in the table below go to documents in PDF format.

Medication Guides are available for these products:

*biologic or drug/biologic combination

- **Abilify (/downloads/Drugs/DrugSafety/ucm085804.pdf)** (aripiprazole) [1/2016 version]
- **Abilify Maintena (/downloads/Drugs/DrugSafety/UCM342207.pdf)** (aripiprazole) [1/2016 version]
- **Absorica (/downloads/Drugs/DrugSafety/UCM306859.pdf)** (isotrentinoin) [2014 version]
- **Abstral (/downloads/Drugs/DrugSafety/UCM239930.pdf)** (fentanyl) [2013 version]
- **Aciphex (/downloads/Drugs/DrugSafety/UCM324059.pdf)** (rabeprazole sodium) [4/2016 version] UPDATED
- **Aciphex DR (/downloads/Drugs/DrugSafety/UCM497380.pdf)** (rabeprazole sodium) [4/2016 version] New!!
- **Accutane (/downloads/Drugs/DrugSafety/ucm085812.pdf)** (isotretinoin) [2010 version]
- **Actemra (/downloads/Drugs/DrugSafety/UCM197463.pdf)*** (tocilizumab) [2013 version]
- **Actiq (/downloads/Drugs/DrugSafety/ucm085817.pdf)** (fentanyl citrate) [2011 version]
- **Actonel (/downloads/Drugs/DrugSafety/UCM241447.pdf)** (risedronate sodium) [2013 version]
- **Actonel with Calcium (/downloads/Drugs/DrugSafety/UCM241449.pdf)** (risedronate sodium and calcium carbonate) [2013 version]
- **Actoplus Met (/downloads/Drugs/DrugSafety/UCM188473.pdf)** (metformin hydrochloride and pioglitazone hydrochloride) [2012 version]
- **Actoplus Met XR (/downloads/Drugs/DrugSafety/UCM170914.pdf)** (metformin hydrochloride and pioglitazone hydrochloride) [2013 version]
- **Actos (/downloads/Drugs/DrugSafety/UCM183833.pdf)** (pioglitazone hydrchloride) [2013 version]
- **Adasuve (/downloads/Drugs/DrugSafety/UCM333532.pdf)** (loxapine) [2012 version]
- **Adderall (/downloads/Drugs/DrugSafety/UCM467750.pdf)**(Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate and Amphetamine Sulfate Tablets) [2015 version]
- **Adderall XR (/downloads/Drugs/DrugSafety/ucm085819.pdf)** (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate) [2013 version]
- **Addyi (/downloads/Drugs/DrugSafety/UCM459254.pdf)**(flibanserin) [2015 version]
- **Adempas (/downloads/Drugs/DrugSafety/UCM372062.pdf)** (riociguat) [2013 version]
- **Advair Diskus (/downloads/Drugs/DrugSafety/ucm111326.pdf)** (fluticasone propionate and salmeterol xinafoate) [4/2014 version]
- **Advair HFA (/downloads/Drugs/DrugSafety/ucm111333.pdf)** (fluticasone propionate and salmeterol xinafoate) [2012 version]
- **Afrezza (/downloads/Drugs/DrugSafety/UCM447695.pdf)** (insulin human) [2015 version]
- **Ambien (/downloads/Drugs/DrugSafety/ucm085906.pdf)** (zolpidem tartrate) [2013 version]
- **Ambien CR (/downloads/Drugs/DrugSafety/ucm085908.pdf)** (zolpidem tartrate) [2013 version]
- **Amevive (/downloads/Drugs/DrugSafety/UCM304191.pdf)*** (alefacept) [2012 version]
- **Ampyra (/downloads/Drugs/DrugSafety/UCM199168.pdf)** (dalfampridine) [2013 version]
- **Anafranil (/downloads/Drugs/DrugSafety/ucm085910.pdf)** (clomipramine hydrochloride) [2012 version]
- **Anaprox (/downloads/Drugs/DrugSafety/ucm085911.pdf)** (naproxen sodium) [2013 version]
- **Androgel (/downloads/Drugs/DrugSafety/UCM188474.pdf)** (1%) (testosterone) [2014 version]
- **Androgel (/downloads/Drugs/DrugSafety/UCM255313.pdf)** (1.62%) (testosterone) [2015 version]
- **AnoroEllipta (/downloads/Drugs/DrugSafety/UCM380278.pdf)** (Umeclidinium; Vilanterol) [2013 version]
- **Mobic (/downloads/Drugs/DrugSafety/ucm088646.pdf)** (meloxicam) [2011 version]
- **Morphabond (/downloads/Drugs/DrugSafety/UCM467785.pdf)** (morphine sulfate)extended release tablets [10/2015]
- **Morphine Sulfate (/downloads/Drugs/DrugSafety/UCM199333.pdf)** (morphine sulfate oral solution) [2011 version]
- **Motrin (/downloads/Drugs/DrugSafety/ucm088647.pdf)** (ibuprofen) [2007 version]
- **Moviprep (/downloads/Drugs/DrugSafety/UCM253840.pdf)** (polyethylene glycol 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid) [2013 version]
- **MS Contin (/downloads/Drugs/DrugSafety/UCM311374.pdf)** (morphine sulfate) [2014 version]
- **Multaq (/downloads/Drugs/DrugSafety/UCM171764.pdf)** (dronedarone) [2014 version]
- **Myfortic (/downloads/Drugs/DrugSafety/UCM172735.pdf)** (mycophenolic acid) [2013 version]
- **Myobloc (/downloads/Drugs/DrugSafety/UCM176361.pdf)*** (rimabotulinumtoxinB) [2009 version]
- **Mysoline (/downloads/Drugs/DrugSafety/UCM222370.pdf)** (primidone) [2010 version]
- **Nalfon (/downloads/Drugs/DrugSafety/ucm088655.pdf)** (fenoprofen calcium) [2009 version]
- **Naprelan (/downloads/Drugs/DrugSafety/UCM280324.pdf)** (naproxen sodium) [2011 version]
- **Naprosyn (/downloads/Drugs/DrugSafety/ucm088657.pdf)** (naproxen) [2013 version]
- **Nardil (/downloads/Drugs/DrugSafety/ucm088660.pdf)** (phenelzine sulfate) [2007 version]
- **Natpara (/downloads/Drugs/DrugSafety/UCM433356.pdf)**(parathyroid hormone) for injection [1/2015 version]
- **Nesina (/downloads/Drugs/DrugSafety/UCM337732.pdf)** (alogliptin) [4/2016 version] UPDATED
- **Neurontin (/downloads/Drugs/DrugSafety/UCM229208.pdf)** (gabapentin) [9/2015 version]
- **Nexium (/downloads/Drugs/DrugSafety/UCM322355.pdf)** (esomeprazole magnesium) [3/2014 version]
- **Nizoral (/downloads/Drugs/DrugSafety/UCM362592.pdf)** (ketoconazole) [2014 version]
- **Nolvadex (/downloads/Drugs/DrugSafety/ucm088661.pdf)** (tamoxifen) [2006 version]
- **Noroxin (/downloads/Drugs/DrugSafety/UCM246795.pdf)** (norfloxacin) [2013 version]
- **Norpramin (/downloads/Drugs/DrugSafety/ucm088665.pdf)** (desipramine hydrochloride) [2014 version]
- **Novantrone (/downloads/Drugs/DrugSafety/UCM297876.pdf)** (mitoXantrone) [2012 version]
- **Nplate (/downloads/Drugs/DrugSafety/UCM088667.pdf)*** (romiplostim) [2014 version]
- **NSAID (/downloads/Drugs/DrugSafety/UCM387559.pdf)** (Nonsteroidal Anti-inflammatory Drugs) [2014 version]
- **Nucynta (http://wcms.fda.gov/downloads/Drugs/DrugSafety/UCM176364.pdf)** (tapentadol hydrochloride) [11/2014 version]
- **Nucynta ER (/downloads/Drugs/DrugSafety/UCM270268.pdf)** (tapentadol) [2014 version]
- **Nulojix (/downloads/Drugs/DrugSafety/UCM261711.pdf)*** (belatacept) [4/2014 version]
- **NuLytely (/downloads/Drugs/DrugSafety/UCM370636.pdf)** (polyethylene glycol 3500, potassium chloride, sodium bicarbonate, and sodium chloride) [2013 version]
- **Nuvigil (/downloads/Drugs/DrugSafety/UCM231717.pdf)** (armodafinil) [4/2015 version]

- **Ansaid (/downloads/Drugs/DrugSafety/ucm085913.pdf)** (flurbiprofen) [2010 version]
- **Aplenzin (/downloads/Drugs/DrugSafety/ucm085915.pdf)** (bupropion hydrobromide [2012 version]
- **Aranesp (/downloads/Drugs/DrugSafety/ucm085918.pdf)*** (darbepoetin alfa) [2012 version)
- **Arcapta (/downloads/Drugs/DrugSafety/UCM263031.pdf)** (indacaterol maleate) [2012 version]
- **Aristada (/downloads/Drugs/DrugSafety/UCM467754.pdf)** (aripiprazole lauroxil) [10/2015 version]
- **Arthrotec (/downloads/Drugs/DrugSafety/ucm085919.pdf)** (diclofenac sodium) [2014 version]
- **Astagraf XL (/downloads/Drugs/DrugSafety/UCM362199.pdf)** (tacrolimus) [2014 version]
- **Atelvia (/downloads/Drugs/DrugSafety/UCM241450.pdf)** (risedronate sodium) [2013 version]
- **Aubagio (/downloads/Drugs/DrugSafety/UCM322204.pdf)** (teriflunomide) [2012 version]
- **Avandamet (/downloads/Drugs/DrugSafety/UCM143419.pdf)** (metformin hydrochloride and rosiglitazone maleate) [5/2014 version]
- **Avandaryl (/downloads/Drugs/DrugSafety/UCM143421.pdf)** (glimepiride and rosiglitazone maleate) [3/2015 version]
- **Avandia (/downloads/Drugs/DrugSafety/ucm085922.pdf)** (rosiglitazone maleate) [5/2014 version]
- **Aveed (/downloads/Drugs/DrugSafety/UCM403061.pdf)** (testosterone undecanoate) [5/2015 version]
- **Avelox (/downloads/Drugs/DrugSafety/UCM231731.pdf)** (moxifloxacin) [2013 version]
- **Avinza (/downloads/Drugs/DrugSafety/UCM311346.pdf)** (morphine sulfate) [2014 version]
- **Avonex (/downloads/Drugs/DrugSafety/ucm085930.pdf)*** (interferon beta-1a) [2012 version]
- **Axiron (/downloads/Drugs/DrugSafety/UCM249396.pdf)** (testosterone) [5/2015 version]
- **Banzel (/downloads/Drugs/DrugSafety/ucm088564.pdf)** (rufinamide) [2011 version]
- **Belbuca (/downloads/Drugs/DrugSafety/UCM470684.pdf)**(buprenorphine) [10/2015 version]
- **Belsomra (/downloads/Drugs/DrugSafety/UCM438475.pdf)** (suvorexant) [2014 version]
- **Benlysta (/downloads/Drugs/DrugSafety/UCM247030.pdf)** (belimumab) [2013 version]
- **Betaseron (/downloads/Drugs/DrugSafety/ucm088565.pdf)***(interferon beta-1b) [2012 version]
- **Binosto (/downloads/Drugs/DrugSafety/UCM318435.pdf)** (alendronate sodium) [2/2015 version]
- **Blincyto (/downloads/Drugs/DrugSafety/UCM426510.pdf)** (blinatumomab) injection [12/2014 version]
- **Boniva (/downloads/Drugs/DrugSafety/UCM241455.pdf)** (ibandronate sodium) Injection [2013 version]
- **Boniva (/downloads/Drugs/DrugSafety/UCM241518.pdf)** (ibandronate sodium) Tablets [3/2015 version]
- **Botox (/downloads/Drugs/DrugSafety/UCM176360.pdf)*** (onabotulinumtoxinA) [1/2016 version]
- **Breo Ellipta (/downloads/Drugs/DrugSafety/UCM352347.pdf)** (fluticasone furoate and vilanterol) [2015 version]
- **Brilinta (/downloads/Drugs/DrugSafety/UCM264220.pdf)** (ticagrelor) [9/2015 version]
- **Brintellix (/downloads/Drugs/DrugSafety/UCM370633.pdf)** (vortioxetine) [2014 version]
- **Brisdelle (/downloads/Drugs/DrugSafety/UCM362200.pdf)** (paroxetine) [12/2014 version]
- **Briviact (((/downloads/Drugs/DrugSafety/UCM493134.pdf)**brivaracetam) [2/2016 version]
- **Odomzo (/downloads/Drugs/DrugSafety/UCM493171.pdf)**(sonidegib) [7/2015]
- **Oleptro (/downloads/Drugs/DrugSafety/UCM202202.pdf)** (trazodone hydrochloride) [2014 version]
- **Omontys (/downloads/Drugs/DrugSafety/UCM297877.pdf)** (peginesatide) [2012 version]
- **Onfi (/downloads/Drugs/DrugSafety/UCM277791.pdf)** (clobazam) [2013 version]
- **Onglyza (/downloads/Drugs/DrugSafety/UCM280356.pdf)** (saxagliptin hydrochloride) [4/2016 version] UPDATED
- **Onsolis (/downloads/Drugs/DrugSafety/UCM285397.pdf)** (fentanyl buccal soluble film) [2011 version]
- **Opana ER (/downloads/Drugs/DrugSafety/UCM283820.pdf)** (oxymorphone hydrochloride) [2014 version]
- **Opdivo (/downloads/Drugs/DrugSafety/UCM438479.pdf)** (nivolumab) [10/2015 version]
- **Opsumit (/downloads/Drugs/DrugSafety/UCM372060.pdf)** (macitentan) [2/2016 version]
- **Oseni (/downloads/Drugs/DrugSafety/UCM337733.pdf)**(alogliptin and pioglitazone) [4/2016 version] UPDATED
- **Osmoprep (/downloads/Drugs/DrugSafety/UCM135936.pdf)** (sodium phosphate dibasic anhydrous and sodium phosphate monobasic monohydrate) [2012 version]
- **Oxtellar XR (/downloads/Drugs/DrugSafety/UCM326087.pdf)** (oxcarbazepine) [2012 version]
- **Oxycodone Hydrochloride Oral Solution (/downloads/Drugs/Drug-Safety/UCM289880.pdf)** [2013 version]
- **OxyContin (/downloads/Drugs/DrugSafety/UCM208530.pdf)** (oxycodone hydrochloride) [2015 version]
- **Oxymorphone Hydrochloride (/downloads/Drugs/DrugSafe-ty/UCM493175.pdf)** [1/2015 version]
- **Pacerone (/downloads/Drugs/DrugSafety/ucm088668.pdf)** (amiodarone hydrochloride) [2008 version]
- **Palladone (/downloads/Drugs/DrugSafety/ucm088670.pdf)** (hydromorphone hydrochloride) [2004 version]
- **Pamelor (/downloads/Drugs/DrugSafety/ucm088671.pdf)** (nortriptyline hydrochloride) [2012 version]
- **Pancreaze (/downloads/Drugs/DrugSafety/UCM208531.pdf)** (pancrelipase) [2014 version]
- **Parnate (/downloads/Drugs/DrugSafety/ucm088674.pdf)** (tranylcypromine sulfate) [2008 version]
- **Paxil (/downloads/Drugs/DrugSafety/ucm088676.pdf)** (paroxetine hydrochloride) [2014 version]
- **Paxil CR (/downloads/Drugs/DrugSafety/UCM249171.pdf)** (paroxetine hydrochloride) [2014 version]
- **Peganone (/downloads/Drugs/DrugSafety/UCM217560.pdf)** (ethotoin) [2010 version]
- **Pegasys (/downloads/Drugs/DrugSafety/ucm088679.pdf)*** (peginterferon alfa-2a) [2014 version]
- **Pegintron (/downloads/Drugs/DrugSafety/UCM133677.pdf)*** (peginterferon alfa-2b) [2013 version]
- **PegIntron*/Rebetol Combo Pack (/downloads/Drugs/DrugSafe-ty/ucm110876.pdf)** (peginterferon alfa-2b and ribavirin) [2008 version]
- **Pennsaid (/downloads/Drugs/DrugSafety/UCM191085.pdf)** (diclofenac sodium) [2014 version]
- **Perforomist (/downloads/Drugs/DrugSafety/UCM214444.pdf)** (formoterol fumarate) [2012 version]
- **Pertzye (/downloads/Drugs/DrugSafety/UCM306861.pdf)** (pancrelipase) [2012 version]
- **Pexeva (/downloads/Drugs/DrugSafety/ucm088684.pdf)** (paroxetine mesylate) [2012 version]
- **Plavix (/downloads/Drugs/DrugSafety/UCM243349.pdf)** (clopidogrel bisulfate) [7/2015 version]

- **Brovana (/downloads/Drugs/DrugSafety/ucm088566.pdf)** (arformoterol tartrate) [2014 version]
- **Bunavail (/downloads/Drugs/DrugSafety/UCM401870.pdf)** (Buprenorphine and naloxone) Buccal Film (6/2014)
- **Butrans (/downloads/Drugs/DrugSafety/UCM219146.pdf)** (buprenorphine) [2014 version]
- **Bydureon (/downloads/Drugs/DrugSafety/UCM289869.pdf)** (exenatide) [32015 version]
- **Byetta (/downloads/Drugs/DrugSafety/UCM191084.pdf)** (exenatide) [2/2015 version]
- **Cambia (/downloads/Drugs/DrugSafety/UCM169077.pdf)** (diclofenac) [2009 version]
- **Caprelsa (/downloads/Drugs/DrugSafety/UCM250399.pdf)** (vandetanib) [3/2014 version]
- **Carbatrol (/downloads/Drugs/DrugSafety/UCM241639.pdf)**(carbamazepine) [2013 version]
- **Cataflam (/downloads/Drugs/DrugSafety/UCM135935.pdf)** (diclofenac potassium) [2011 version]
- **Celebrex (/downloads/Drugs/DrugSafety/ucm088567.pdf)** (celecoxib) [8/2015 version]
- **Celexa (/downloads/Drugs/DrugSafety/ucm088568.pdf)** (citalopram hydrobromide) [4/2014 version]
- **Cellcept (/downloads/Drugs/DrugSafety/UCM170919.pdf)** (mycophenolate mofetil) [2013 version]
- **Celontin (/downloads/Drugs/DrugSafety/UCM229201.pdf)** (methsuximide) [2010 version]
- **Chantix (/downloads/Drugs/DrugSafety/ucm088569.pdf)** (varenicline tartrate) [9/2014 version]
- **Cimzia (/downloads/Drugs/DrugSafety/ucm088571.pdf)*** (certolizumab pegol) [2013 version]
- **Cipro (/downloads/Drugs/DrugSafety/UCM246794.pdf)** (ciprofloxacin) [2015 version]
- **Clinoril (/downloads/Drugs/DrugSafety/ucm088573.pdf)** (sulindac) [2010 version]
- **Codeine Sulfate (/downloads/Drugs/DrugSafety/UCM302557.pdf)** oral solution [2013 version]
- **Colcrys (/downloads/Drugs/DrugSafety/UCM176363.pdf)** (colchicine) [2011 version]
- **Combunox (/downloads/Drugs/DrugSafety/ucm088574.pdf)** (oxycodone hydrochloride and ibuprofen) [2010 version]
- **Concerta (/downloads/Drugs/DrugSafety/ucm088575.pdf)** (methylphenidate hydrochloride) [2013 version]
- **Copegus (/downloads/Drugs/DrugSafety/ucm088576.pdf)** (ribavirin) [2011 version]
- **Cordarone (/downloads/Drugs/DrugSafety/UCM152841.pdf)** (amiodarone hydrochloride) [2011 version]
- **Cosentyx (/downloads/Drugs/DrugSafety/UCM433352.pdf)**(secukinumab) [2015 version]
- **Coumadin (/downloads/Drugs/DrugSafety/ucm088578.pdf)** (warfarin sodium) [2011 version]
- **Creon (/downloads/Drugs/DrugSafety/UCM152847.pdf)** (pancrelipase) [2012 version]
- **Cymbalta (/downloads/Drugs/DrugSafety/ucm088579.pdf)** (duloxetine hydrochloride) [2014 version)]
- **Daliresp (/downloads/Drugs/DrugSafety/UCM286063.pdf)** (roflumilast) [2013 version]
- **Dalmane (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/016721s077lbl.pdf)** (flurazepam hydrochloride) [2009 version]
- **Darvocet (/downloads/Drugs/DrugSafety/UCM187067.pdf)** (acetaminophen and propoxyphene napsylate) [2009 version]
- **Darvon (/downloads/Drugs/DrugSafety/UCM187068.pdf)** (propoxyphene hydrochloride) [2009 version]
- **Daypro Alta (/downloads/Drugs/DrugSafety/ucm088580.pdf)** (oxaprozin potassium) [2007 version]
- **Plegridy (/downloads/Drugs/DrugSafety/UCM475804.pdf)** (peginterferon beta-1a) [8/2014 version]
- **Pomalyst (/downloads/Drugs/DrugSafety/UCM340163.pdf)** (pomalidomide) [4/2015 version]
- **Ponstel (/downloads/Drugs/DrugSafety/ucm088692.pdf)** (mefenamic acid) [2008 version]
- **Potiga (/downloads/Drugs/DrugSafety/UCM259619.pdf)** (ezogabine) [2013 version]
- **Pradaxa (/downloads/Drugs/DrugSafety/UCM231720.pdf)**(dabigatran etexilate mesylate) [2015 version]
- **Prepopik (/downloads/Drugs/DrugSafety/UCM312633.pdf)**(sodium picosulfate, magnesium oxide and citric acid) [2012 version]
- **Prevacid (/downloads/Drugs/DrugSafety/UCM322354.pdf)** (lansoprazole [12/2015 version]
- **Prevacid NapraPac (/downloads/Drugs/DrugSafety/ucm088694.pdf)** (lansoprazole and naproxen) [5/2019 version]
- **Priftin (/downloads/Drugs/DrugSafety/UCM426514.pdf)**(rifapentine) Tablets [11/2014 version]
- **Prilosec (/downloads/Drugs/DrugSafety/UCM322359.pdf)** (omeprazole [2016 version]
- **Pristiq (/downloads/Drugs/DrugSafety/UCM088985.pdf)** (desvenlafaxine succinate) [2014 version]
- **Procrit (/downloads/Drugs/DrugSafety/ucm088988.pdf)*** (epoetin alfa) [2012 version]
- **Prolia (/downloads/Drugs/DrugSafety/UCM214385.pdf)*** (denosumab) [2/2015 version]
- **Propylthiouracil (/downloads/Drugs/DrugSafety/UCM208533.pdf)** [2010 version]
- **Promacta (/downloads/Drugs/DrugSafety/ucm088990.pdf)** (eltrombopag) [8/2014 version]
- **Propulsid (/downloads/Drugs/DrugSafety/ucm088994.pdf)** (cisapride) [2006 version]
- **Proquin XR (/downloads/Drugs/DrugSafety/UCM239933.pdf)** (ciprofloxacin hydrochloride) [2011 version]
- **Protonix (/downloads/Drugs/DrugSafety/UCM324058.pdf)** (pantoprazole sodium) [2013 version]
- **Protopic Ointment (/downloads/Drugs/DrugSafety/ucm088996.pdf)** (tacrolimus) [2011 version]
- **Provigil (/downloads/Drugs/DrugSafety/UCM231722.pdf)** (modafinil) [2015 version]
- **Prozac (/downloads/Drugs/DrugSafety/ucm088999.pdf)** (fluoxetine hydrochloride) [2013 version]
- **Qsymia (/downloads/Drugs/DrugSafety/UCM312590.pdf)** (phentermine and topiramate) [9/2014 version]
- **Qualaquin (/downloads/Drugs/DrugSafety/UCM192698.pdf)** (quinine sulfate) [2014 version]
- **Qudexy XR (/downloads/Drugs/DrugSafety/UCM389283.pdf)** (topiramate) [2014 version]
- **QuilliChew (/downloads/Drugs/DrugSafety/UCM493191.pdf)** (methylphenidate Hydorchloride) [12/2015 version]
- **Quillivant XR (/downloads/Drugs/DrugSafety/UCM322209.pdf)** (methylphenidate) [2/2015 version]
- **Rapamune (/downloads/Drugs/DrugSafety/UCM235958.pdf)** (sirolimus) [2013 version]
- **Ravicti (/downloads/Drugs/DrugSafety/UCM338056.pdf)**(glycerol phenylbutyrate) [2013 version]
- **Rebetol (/downloads/Drugs/DrugSafety/ucm089017.pdf)** (ribavirin) [2013 version]
- **Rebif (/downloads/Drugs/DrugSafety/ucm089019.pdf)*** (interferon beta-1a) [4/2014 version]
- **Reclast (/downloads/Drugs/DrugSafety/UCM241522.pdf)** (zoledronic acid) [1/2015 version]

- **Daytrana (/downloads/Drugs/DrugSafety/ucm088581.pdf)** (methylphenidate) [2013 version]
- **Depakene (/downloads/Drugs/DrugSafety/UCM342868.pdf)** (valproic acid) [2/2016 version]
- **Depakote (/downloads/Drugs/DrugSafety/UCM342868.pdf)** ER(divalproex sodium) [2/2016 version]
- **Desoxyn (/downloads/Drugs/DrugSafety/ucm088582.pdf)** (methamphetamine hydrochloride) [2013 version]
- **Desvenlafaxine (/downloads/Drugs/DrugSafety/UCM372058.pdf)** Extended Release Tablet(desvenlafaxine fumarate) [2014 version]
- **Dexedrine (/downloads/Drugs/DrugSafety/ucm088583.pdf)** (dextroamphetamine sulfate) [2013 version]
- **Dexilant (/downloads/Drugs/DrugSafety/UCM322208.pdf)** (dexlansoprazole) [2016 version]
- **Dilantin (/downloads/Drugs/DrugSafety/UCM241523.pdf)** (phenytoin) [2011 version]
- **Dilantin-125 (/downloads/Drugs/DrugSafety/UCM283845.pdf)** (phenytoin) [2014 version]
- **Dolophine (/downloads/Drugs/DrugSafety/UCM311370.pdf)** (methadone hydrochloride) [2014 version]
- **Doral (/downloads/Drugs/DrugSafety/UCM191086.pdf)** (quazepam) [2013 version]
- **Duetact (/downloads/Drugs/DrugSafety/UCM227815.pdf)** (glimepiride and pioglitazone) [3/2015 version]
- **Duexis (/downloads/Drugs/DrugSafety/UCM253076.pdf)** (ibuprofen and famotidine) [2011 version]
- **Dulera (/downloads/Drugs/DrugSafety/UCM217561.pdf)** (mometasone furoate and formoterol fumarate) [4/2015 version]
- **Duragesic (/downloads/Drugs/DrugSafety/ucm088584.pdf)** (fentanyl) [2014 version]
- **Dysport (/downloads/Drugs/DrugSafety/UCM165110.pdf)*** (abobotulinumtoxinA) [7/2015 version]
- **EC-Naprosyn (/downloads/Drugs/DrugSafety/ucm088585.pdf)** (naproxen) [2013 version]
- **Edluar (/downloads/Drugs/DrugSafety/UCM135937.pdf)** (zolpidem tartrate) [2013 version]
- **Effexor (/downloads/Drugs/DrugSafety/ucm088586.pdf)** (venlafaxine hydrochloride) [2012 version]
- **Effexor XR (/downloads/Drugs/DrugSafety/UCM192697.pdf)** (venlafaxine hydrochloride) [2012 version]
- **Effient (/downloads/Drugs/DrugSafety/UCM238428.pdf)** (prasugrel) [1/2016 version]
- **Elidel Cream (/downloads/Drugs/DrugSafety/ucm088587.pdf)**(pimecrolimus) [3/2014 version]
- **Eliquis (/downloads/Drugs/DrugSafety/UCM333961.pdf)**(apixaban) [6/2015 version]
- **Embeda (/downloads/Drugs/DrugSafety/UCM179172.pdf)** (morphine sulfate and naltrexone hydrochloride) [2014 version]
- **Emsam (/downloads/Drugs/DrugSafety/ucm088589.pdf)** (selegeline transdermal system) [2007 version]
- **Enbrel (/downloads/Drugs/DrugSafety/ucm088590.pdf)*** (etanercept) [2013 version]
- **Entyvio (/downloads/Drugs/DrugSafety/UCM491477.pdf)**(vedolizumab) [2014 version]
- **Epogen (/downloads/Drugs/DrugSafety/ucm088591.pdf)*** (epoetin alfa) [2012 version]
- **Epzicom (/downloads/Drugs/DrugSafety/ucm088592.pdf)** (abacavir sulfate and lamivudine) [9/2015 version]
- **Equetro (/downloads/Drugs/DrugSafety/UCM328348.pdf)** (carbamazepine) [2012 version]
- **Erivedge (/downloads/Drugs/DrugSafety/UCM289871.pdf)** (vismodegib) [2012 version]
- **Estazolam (/downloads/Drugs/DrugSafety/UCM359235.pdf)** [2008 version]
- **Reglan (/downloads/Drugs/DrugSafety/UCM176362.pdf)** (metoclopramide hydrochloride) injection [2009 version]
- **Reglan (/downloads/Drugs/DrugSafety/UCM235574.pdf)** (metoclopramide hydrochloride) tablets [2011 version]
- **Reglan ODT (/downloads/Drugs/DrugSafety/UCM183841.pdf)** (metoclopramide hydrochloride) [2011 version]
- **Relistor (/downloads/Drugs/DrugSafety/UCM417497.pdf)** (methylnaltrexone bromide) [9/2014 version]
- **Remeron (/downloads/Drugs/DrugSafety/ucm089021.pdf)** (mirtazapine) [2014 version]
- **Remeron SolTab (/downloads/Drugs/DrugSafety/UCM289881.pdf)** (mirtazapine) [2014 version]
- **Remicade (/downloads/Drugs/DrugSafety/ucm089023.pdf)*** (infliximab) [10/2015 version]
- **Restoril (/downloads/Drugs/DrugSafety/UCM233806.pdf)** (temazepam) [2010 version]
- **Revlimid (/downloads/Drugs/DrugSafety/ucm111335.pdf)** (lenalidomide) [2014 version]
- **Ribasphere (/downloads/Drugs/DrugSafety/ucm111342.pdf)** (ribavirin) [2008 version]
- **Ritalin (/downloads/Drugs/DrugSafety/ucm089090.pdf)** (methylphenidate hydrochloride) [2015 version]
- **Ritalin LA (/downloads/Drugs/DrugSafety/ucm089092.pdf)** (methylphenidate hydrochloride) [2013 version]
- **Ritalin-SR (/downloads/Drugs/DrugSafety/ucm089095.pdf)** (methylphenidate hydrochloride) [2015 version]
- **Rituxan (/downloads/Drugs/DrugSafety/UCM169892.pdf)*** (rituximab) [2013 version]
- **Roferon-A (/downloads/Drugs/DrugSafety/ucm111340.pdf)*** (interferon alfa-2a recombinant) [2008 version]
- **Rozerem (/downloads/Drugs/DrugSafety/UCM143463.pdf)** (ramelteon) [2010 version]
- **Sabril (/downloads/Drugs/DrugSafety/UCM180720.pdf)** (vigabatrin) [2013 version]
- **Samsca (/downloads/Drugs/DrugSafety/UCM235540.pdf)** (tolvaptan) [2014 version]
- **Sarafem (/downloads/Drugs/DrugSafety/ucm089119.pdf)** (fluoxetine hydrochloride) [10/2014 version]
- **Savaysa (/downloads/Drugs/DrugSafety/UCM467811.pdf)**(edoxaban) tablets [2015 version]
- **Savella (/downloads/Drugs/DrugSafety/ucm089121.pdf)** (milnacipran hydrochloride) [1/2015 version]
- **Saxenda (liraglutide) (/downloads/Drugs/DrugSafety/UCM487804.pdf)** injection [2014 version]
- **Selzentry (/downloads/Drugs/DrugSafety/ucm089122.pdf)** (maraviroc) [3/2014 version]
- **Serevent Diskus (/downloads/Drugs/DrugSafety/ucm089125.pdf)** (salmeterol xinafoate) [4/2014 version]
- **Seroquel (/downloads/Drugs/DrugSafety/ucm089126.pdf)** (quetiapine fumarate) [2013 version]
- **Seroquel XR (/downloads/Drugs/DrugSafety/UCM194582.pdf)** (quetiapine fumarate) [2013 version]
- **Signifor (/downloads/Drugs/DrugSafety/UCM332633.pdf)** (pasireotide diaspartate) [3/2015 version]
- **Silenor (/downloads/Drugs/DrugSafety/UCM206668.pdf)** (doxepin) [2010 version]
- **Simponi (/downloads/Drugs/DrugSafety/UCM152822.pdf)*** (golimumab) [1/2016 version]
- **Simponi Aria (/downloads/Drugs/DrugSafety/UCM362202.pdf)*** (golimumab) [1/2016 version]
- **Sinequan (/downloads/Drugs/DrugSafety/ucm089129.pdf)** (doxepin hydrochloride) [2007 version]
- **Sirturo (/downloads/Drugs/DrugSafety/UCM333729.pdf)** (bedaquiline) [2013 version]

- **Evista (/downloads/Drugs/DrugSafety/ucm088593.pdf)** (raloxifene hydrochloride) [2007 version]
- **Exalgo (/downloads/Drugs/DrugSafety/UCM204267.pdf)** (hydromorphone hydrochloride) [2014 version]
- **Extavia (/downloads/Drugs/DrugSafety/UCM180718.pdf)*** (interferon beta-1b) [2012 version]
- **Extraneal (/downloads/Drugs/DrugSafety/UCM135933.pdf)** (icodextrin) [2010 version]
- **Exubera (/downloads/Drugs/DrugSafety/ucm088594.pdf)** (insulin recombinant human) [2008 version]
- **Factive (/downloads/Drugs/DrugSafety/UCM152723.pdf)** (gemifloxacin) [2013 version]
- **Farxiga (/downloads/Drugs/DrugSafety/UCM439564.pdf)** (dapagliflozin) [1/2016 version]
- **Farydak (panobinostat) (/downloads/Drugs/DrugSafety/UCM436377.pdf)** [2/2015 version]
- **Felbatol (/downloads/Drugs/DrugSafety/UCM263034.pdf)** (felbamate) [2011 version]
- **Feldene (/downloads/Drugs/DrugSafety/ucm088596.pdf)** (piroxicam) [2010 version]
- **Fentora (/downloads/Drugs/DrugSafety/ucm088597.pdf)** (fentanyl citrate) [2013 version]
- **Ferriprox (/downloads/Drugs/DrugSafety/UCM302558.pdf)**(deferiprone) [2012 version]
- **Fetzima (/downloads/Drugs/DrugSafety/UCM406944.pdf)** (levomilnacipran) [2014 version]
- **Flector (/downloads/Drugs/DrugSafety/ucm088598.pdf)** (diclofenac epolamine) [2010 version]
- **Floxin (/downloads/Drugs/DrugSafety/ucm088599.pdf)** (ofloxacin) [2011 version]
- **Fluoxetine (/downloads/Drugs/DrugSafety/UCM406910.pdf)** (Fluoxetine) [2014 version]
- **Focalin (/downloads/Drugs/DrugSafety/ucm088600.pdf)** (dexmethylphenidate hydrochloride) [2013 version]
- **Focalin XR (/downloads/Drugs/DrugSafety/ucm088601.pdf)** (dexmethylphenidate hydrochloride) [2013 version]
- **Foradil Aerolizer (/downloads/Drugs/DrugSafety/ucm088602.pdf)** (formoterol fumarate inhalation powder) [2012 version]
- **Foradil Certihaler (/downloads/Drugs/DrugSafety/ucm088603.pdf)** (formoterol fumarate inhalation powder) [2010 version]
- **Forfivo XL (/downloads/Drugs/DrugSafety/UCM280358.pdf)** (bupropion hydrochloride) [2014 version]
- **Forteo (/downloads/Drugs/DrugSafety/ucm088604.pdf)** (teriparatide) [2013 version]
- **Fortesta (/downloads/Drugs/DrugSafety/UCM239932.pdf)** (testosterone) [5/2015 version]
- **Fosamax (/downloads/Drugs/DrugSafety/UCM241519.pdf)** (alendronate sodium) [2013 version]
- **Fosamax Plus D (/downloads/Drugs/DrugSafety/UCM241521.pdf)** (alendronate sodium and cholecalciferol) [2013 version]
- **Fosrenol (/downloads/Drugs/DrugSafety/UCM271798.pdf)** (lanthanum carbonate) [9/2014 version]
- **Fycompa (/downloads/Drugs/DrugSafety/UCM326088.pdf)** (perampanel) [2014 version]
- **Gabitril (/downloads/Drugs/DrugSafety/UCM229203.pdf)** (tiagabine) [2010 version]
- **Gattex (/downloads/Drugs/DrugSafety/UCM333533.pdf)** (teduglutide [rDNA origin]) [2012 version]
- **Gilenya (/downloads/Drugs/DrugSafety/UCM227569.pdf)** (fingolimid) [2/2016 version]
- **Glyxambi (/downloads/Drugs/DrugSafety/UCM433353.pdf)** (empagliflozin and linagliptin) Tablets [1/2015 version]
- **GoLytely (/downloads/Drugs/DrugSafety/UCM370635.pdf)** (polyethylene glycol 3500, potassium chloride, sodium bicarbonate, sodium chloride, and sodium sulfate anhydrous) [2013 version]
- **Soliris (/downloads/Drugs/DrugSafety/ucm089130.pdf)*** (eculizumab) [12/2015 version] UPDATED
- **Soltamox (/downloads/Drugs/DrugSafety/ucm089131.pdf)** (tamoxifen citrate) [2005 version]
- **Sonata (/downloads/Drugs/DrugSafety/UCM349707.pdf)** (zaleplon) [2013 version]
- **Soriatane (/downloads/Drugs/DrugSafety/ucm089133.pdf)** (acitretin) [2014 version]
- **Sotret (/downloads/Drugs/DrugSafety/ucm089135.pdf)** (isotretinoin) [2006 version]
- **Spritam (levetiracetam) (/downloads/Drugs/DrugSafety/UCM487803.pdf)** tablets [2/2016 version]
- **Stavzor (/downloads/Drugs/DrugSafety/UCM342867.pdf)** (valproic acid) [2013 version]
- **Stelara (/downloads/Drugs/DrugSafety/UCM187066.pdf)*** (ustekinumab) [2014 version]
- **Strattera (/downloads/Drugs/DrugSafety/ucm089138.pdf)** (atomoxetine hydrochloride) [2014 version]
- **Suboxone (/downloads/Drugs/DrugSafety/UCM225677.pdf)** (buprenorphine and naloxone) [9/2015 version]
- **Subsys (/downloads/Drugs/DrugSafety/UCM287863.pdf)** (fentanyl) [2012 version]
- **Subutex (/downloads/Drugs/DrugSafety/UCM285300.pdf)** (buprenorphine) [2011 version]
- **Suclear (/downloads/Drugs/DrugSafety/UCM337734.pdf)**(sodium sulfate, potassium sulfate, magnesium sulfate, sodium chloride, sodium bicarbonate, and potassium chloride) [2013 version]
- **Suprep (/downloads/Drugs/DrugSafety/UCM222368.pdf)** (sodium sulfate, potassium sulfate and magnesium sulfate) [2010 version]
- **Surmontil (/downloads/Drugs/DrugSafety/UCM330750.pdf)** (trimipramine) [2014 version]
- **Sutent (/downloads/Drugs/DrugSafety/UCM219111.pdf)** (sunitimib malate) [2013 version]
- **Sylatron (/downloads/Drugs/DrugSafety/UCM249397.pdf)** (peginterferon alfa-2b) [5/2015 version]
- **Symbicort (/downloads/Drugs/DrugSafety/ucm089139.pdf)** (budesonide and formoterol fumarate dihydrate) [2010 version]
- **Symbyax (/downloads/Drugs/DrugSafety/ucm089140.pdf)** (fluoxetine hydrochloride and olanzapine) [2014 version]
- **Symlin (/downloads/Drugs/DrugSafety/ucm089141.pdf)** (pramlintide acetate) [2007 version]
- **Synribo (/downloads/Drugs/DrugSafety/UCM396919.pdf)** (omacetaxine mepesuccinate) [4/2014 version]
- **Tafinlar (/downloads/Drugs/DrugSafety/UCM354532.pdf)** (dabrafenib) [2013 version]
- **Taltz (/downloads/Drugs/DrugSafety/UCM493178.pdf)**(ixekizumab) [3/2016]
- **Tanzeum (/downloads/Drugs/DrugSafety/UCM448173.pdf)** (albiglutide) [3/2015 version]
- **Tapentadol (/downloads/Drugs/DrugSafety/ucm092188.pdf)** see Nucynta
- **Targiniq ER (/downloads/Drugs/DrugSafety/UCM411076.pdf)** (oxycodone hydrochloride and naloxone hydrochloride extended-release tablets) [2014 version]
- **Tasigna (/downloads/Drugs/DrugSafety/UCM089159.pdf)** (nilotinib) [1/2015 version]
- **Technivie (/downloads/Drugs/DrugSafety/UCM486199.pdf)** (ombitasvir, paritaprevir and ritonavir tablets) [1/2016 version]
- **Tegretol and Tegretol XR (/downloads/Drugs/DrugSafety/UCM246796.pdf)**(carbamazepine) [2014 version]
- **Testim (/downloads/Drugs/DrugSafety/UCM188475.pdf)** (testosterone) [5/2015 version]

- **Gralise (/downloads/Drugs/DrugSafety/UCM245196.pdf)** (gabapentin) [2012 version]
- **Halcion (/downloads/Drugs/DrugSafety/ucm088610.pdf)** (triazolam) [9/2014 version]
- **HalfLytely and Bisacodyl Bowel Prep Kit (/downloads/Drugs/DrugSafety/UCM220644.pdf)** (bisacodyl, polyethylene glycol 3500, potassium chloride, sodium bicarbonate, and sodium chloride) [2010 version]
- **Horizant (/downloads/Drugs/DrugSafety/UCM250398.pdf)** (gabapentin enacarbil) [2013 version]
- **H.P. Acthar Gel (/downloads/Drugs/DrugSafety/UCM231714.pdf)** (repository corticotropin) [2010 version]
- **Humira (/downloads/Drugs/DrugSafety/ucm088611.pdf)*** (adalimumab) [2013 version]
- **Hydromorphone Hydrochloride ER (/downloads/Drugs/DrugSafety/UCM403064.pdf)** [2014 version]
- **Hysingla ER (/downloads/Drugs/DrugSafety/UCM433047.pdf)** (Hydrocodone, Bitartrate) [2014 version]
- **Incivek (/downloads/Drugs/DrugSafety/UCM256383.pdf)** (telaprevir) [2013 version]
- **Inflectra (/downloads/Drugs/DrugSafety/UCM497384.pdf)** (Infliximab-dyyb) [4/2016 version] New!!
- **Iclusig (/downloads/Drugs/DrugSafety/UCM333534.pdf)**(ponatinib) [2013 version]
- **Ilaris (/downloads/Drugs/DrugSafety/UCM352352.pdf)*** (canakinumab) [2013 version]
- **Impavido (/downloads/Drugs/DrugSafety/UCM390972.pdf)** (miltefosine) [2014 version]
- **Indocin (/downloads/Drugs/DrugSafety/ucm088612.pdf)** (indomethacin) [2008 version]
- **Infergen (/downloads/Drugs/DrugSafety/ucm088613.pdf)*** (interferon alfacon-1) [2013 version]
- **Intermezzo (/downloads/Drugs/DrugSafety/UCM281854.pdf)** (zolpidem tartrate) [2013 version]
- **Intron A (/downloads/Drugs/DrugSafety/ucm111337.pdf)*** (interferon alfa-2b) [4/2014 version]
- **Invirase (/downloads/Drugs/DrugSafety/UCM229206.pdf)** (saquinavir mesylate) [12/2016 version]
- **Invokamet (/downloads/Drugs/DrugSafety/UCM470691.pdf)** (canagliflozin and metformin hydrochloride) [8/2015]
- **Invokana (/downloads/Drugs/DrugSafety/UCM346637.pdf)** (canagliflozin) [3/2016 version]
- **Janumet (/downloads/Drugs/DrugSafety/UCM204268.pdf)** (metformin hydrochloride and sitagliptin phosphate) [2013 version]
- **Janumet XR (/downloads/Drugs/DrugSafety/UCM291878.pdf)** (sitagliptin and metformin hydrochloride) [2014 version]
- **Januvia (/downloads/Drugs/DrugSafety/UCM204269.pdf)** (sitagliptin phosphate) [2013 version]
- **Jentadueto (/downloads/Drugs/DrugSafety/UCM359031.pdf)** (linagliptin and metformin hydrochloride) [2013 version]
- **Juvisync (/downloads/Drugs/DrugSafety/UCM275945.pdf)** (sitagliptin and simvastatin) [2014 version]
- **Juxtapid (/downloads/Drugs/DrugSafety/UCM333530.pdf)** (lomitapide) [4/2015 version]
- **Kadian (/downloads/Drugs/DrugSafety/UCM311373.pdf)** (morphine sulfate) [2014 version]
- **Kalbitor (/downloads/Drugs/DrugSafety/UCM192722.pdf)*** (ecallantide) [3/2014 version]
- **Kaletra (/downloads/Drugs/DrugSafety/UCM143461.pdf)**Capsules (lopinavir and ritonavir) [2013 version]
- **Kaletra (/downloads/Drugs/DrugSafety/UCM310187.pdf)**Tablets and Oral Solution (lopinavir and ritonavir) [1/2015 version]
- **Kazano (/downloads/Drugs/DrugSafety/UCM337729.pdf)** (alogliptin and metformin hydrochloride) [4/2016 version] UPDATED
- **Testosterone Gel (Perrigo) (/downloads/Drugs/DrugSafety/UCM294248.pdf)** [5/2015 version]
- **Testosterone Gel (/downloads/Drugs/DrugSafety/UCM403065.pdf)** (Teva) [5/2015 version]
- **Thalomid (/downloads/Drugs/DrugSafety/UCM222363.pdf)** (thalidomide) [2014 version]
- **Tikosyn (/downloads/Drugs/DrugSafety/UCM266314.pdf)** (dofetilide) [2013 version]
- **Tofranil (/downloads/Drugs/DrugSafety/ucm089161.pdf)** (imipramine hydrochloride) [2007 version]
- **Tofranil-PM (/downloads/Drugs/DrugSafety/UCM326090.pdf)** (imipramine pamoate) [2012 version]
- **Tolectin (/downloads/Drugs/DrugSafety/ucm089162.pdf)** (tolmetin sodium) [2008 version]
- **Topamax (/downloads/Drugs/DrugSafety/UCM152837.pdf)** (topiramate) [3/2014 version]
- **Toradol (/downloads/Drugs/DrugSafety/ucm089165.pdf)** (ketorolac tromethamine) [2013 version]
- **Tracleer (/downloads/Drugs/DrugSafety/ucm089801.pdf)** (bosentan) [12/2015 version]
- **Tradjenta (/downloads/Drugs/DrugSafety/UCM359033.pdf)** (linagliptin) [2013 version]
- **Tranxene (/downloads/Drugs/DrugSafety/UCM217562.pdf)** (clorazepate dipotassium) [2010 version]
- **Treximet (/downloads/Drugs/DrugSafety/ucm089804.pdf)** (naproxen sodium and sumatriptan succinate) [2012 version]
- **Tridione (/downloads/Drugs/DrugSafety/UCM308402.pdf)** (trimethadione) [2012 version]
- **Trileptal (/downloads/Drugs/DrugSafety/UCM246799.pdf)** (oxcarbazepine) [2011 version]
- **Trilipix (/downloads/Drugs/DrugSafety/ucm089806.pdf)** (choline fenofibrate) [2012 version]
- **Triumeq (/downloads/Drugs/DrugSafety/UCM467819.pdf)**(abacavir, dolutegravir, and lamivudine) tablets [2015 version]
- **Trizivir (/downloads/Drugs/DrugSafety/ucm089807.pdf)** (abacavir sulfate, lamivudine and zidovudine) [9/2015 version]
- **Trokendi XR (/downloads/Drugs/DrugSafety/UCM366909.pdf)** (topiramate) [2013 version]
- **Truvada (/downloads/Drugs/DrugSafety/UCM312307.pdf)** (emtricitabine and tenofovir disoproxil fumarate) [2013 version]
- **Tysabri (/downloads/Drugs/DrugSafety/ucm089809.pdf)** (natalizumab) [5/2015 version]
- **Tyzeka (/downloads/Drugs/DrugSafety/UCM135934.pdf)** (telbivudine) [2013 version]
- **Ultresa (/downloads/Drugs/DrugSafety/UCM296221.pdf)** (pancrelipase) [2012 version]
- **Valchlor (/downloads/Drugs/DrugSafety/UCM366908.pdf)** (mechlorethamine) [2013 version]
- **Vandetanib (/downloads/Drugs/DrugSafety/UCM250399.pdf)** see Caprelsa
- **Venclexta (/downloads/Drugs/DrugSafety/UCM497391.pdf)** (venetoclax) [4/2016 version] New!!
- **Venlafaxine HCl ER (/downloads/Drugs/DrugSafety/UCM406909.pdf)** (venlafaxine hydrochloride) [2014 version]
- **Vibativ (/downloads/Drugs/DrugSafety/UCM183838.pdf)** (telavancin) [12/2014 version]
- **Vicoprofen (/downloads/Drugs/DrugSafety/ucm089815.pdf)** (hydrocodone bitartrate and ibuprofen) [2008 version]
- **Victoza (/downloads/Drugs/DrugSafety/UCM199170.pdf)** (liraglutide) [2013 version]
- **Victrelis (/downloads/Drugs/DrugSafety/UCM255471.pdf)** (boceprevir) [2014 version]
- **Videx (/downloads/Drugs/DrugSafety/UCM199211.pdf)** (didanosine) [2011 version]

- **Keppra (/downloads/Drugs/DrugSafety/UCM152832.pdf)** (levetiracetam) [2013 version]
- **Keppra XR (/downloads/Drugs/DrugSafety/UCM312880.pdf)** (levetiracetam) [4/2016 version] UPDATED
- **Ketek (/downloads/Drugs/DrugSafety/ucm088615.pdf)** (telithromycin) [2010 version]
- **Keytruda (/downloads/Drugs/DrugSafety/UCM417493.pdf)**(pembrolizumab) [10/2015 version]
- **Khedezla (/downloads/Drugs/DrugSafety/UCM362206.pdf)** (desvenlafaxine) [2013 version]
- **Klonopin (/downloads/Drugs/DrugSafety/UCM225680.pdf)** (clonazepam) [2013 version]
- **Kombiglyze XR (/downloads/Drugs/DrugSafety/UCM280360.pdf)** (metformin hydrochloride and saxagliptin) [4/2016 version] UPDATED
- **Korlym (/downloads/Drugs/DrugSafety/UCM294245.pdf)** (mifepristone) [2012 version]
- **Krystexxa (/downloads/Drugs/DrugSafety/UCM227568.pdf)*** (pegloticase) [2012 version]
- **Kynamro (/downloads/Drugs/DrugSafety/UCM337730.pdf)** (mipomersen sodium) [5/2014 version]
- **Lamictal (/downloads/Drugs/DrugSafety/UCM152835.pdf)** (lamotrigine) [2013 version]
- **Lamictal XR (/downloads/Drugs/DrugSafety/UCM166013.pdf)** (lamotrigine) [2013 version]
- **Lariam (/downloads/Drugs/DrugSafety/ucm088616.pdf)** (mefloquine hydrochloride) [2009 version]
- **Latuda (/downloads/Drugs/DrugSafety/UCM362201.pdf)** (lurasidone hydrochloride) [2013 version]
- **Lazanda (/downloads/Drugs/DrugSafety/UCM263032.pdf)** (fentanyl citrate) [2011 version]
- **Lemtrada (/downloads/Drugs/DrugSafety/UCM426512.pdf)**(alemtuzumab) Injection [11/2014 version]
- **Letairis (/downloads/Drugs/DrugSafety/ucm088617.pdf)** (ambrisentan) [10/2015 version]
- **Levaquin (/downloads/Drugs/DrugSafety/ucm088619.pdf)** (levofloxacin) [2013 version]
- **Lexapro (/downloads/Drugs/DrugSafety/ucm088620.pdf)** (escitalopram oxalate) [1/2016 version]
- **Limbitrol (/downloads/Drugs/DrugSafety/ucm088622.pdf)** (chlordiazepoxide and amitriptyline) [2007 version]
- **Lindane Lotion (/downloads/Drugs/DrugSafety/UCM133687.pdf)** (lindane) [2007 version]
- **Lindane Shampoo (/downloads/Drugs/DrugSafety/UCM133688.pdf)** (lindane) [2007 version]
- **Linzess (/downloads/Drugs/DrugSafety/UCM318437.pdf)** (linaclotide) [11/2016 version] UPDATED
- **Lotronex (/downloads/Drugs/DrugSafety/ucm088624.pdf)** (alosetron hydrochloride) [/2016 version]
- **Lunesta (/downloads/Drugs/DrugSafety/UCM134691.pdf)** (eszopiclone) [2014 version]
- **Luvox (/downloads/Drugs/DrugSafety/UCM249169.pdf)** (fluvoxamine maleate) [2014 version]
- **Luvox CR (/downloads/Drugs/DrugSafety/ucm088625.pdf)** (fluvoxamine maleate) [2014 version]
- **Lynparza (/downloads/Drugs/DrugSafety/UCM438477.pdf)** (olaparib) [2014 version]
- **Lyrica (/downloads/Drugs/DrugSafety/UCM152825.pdf)** (pregabalin) [2013 version]
- **Marplan (/downloads/Drugs/DrugSafety/ucm088633.pdf)** (isocarboxazid) [2008 version]
- **Meridia (/downloads/Drugs/DrugSafety/UCM222366.pdf)** (sibutramine hydrochloride) [2010 version]
- **Metadate CD (/downloads/Drugs/DrugSafety/ucm088635.pdf)** (methylphenidate hydrochloride) [6/2014 version]
- **Videx EC (/downloads/Drugs/DrugSafety/UCM199212.pdf)** (didanosine) [2011 version]
- **Viekira Pak (/downloads/Drugs/DrugSafety/UCM467825.pdf)** ((ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets) [1/2016 version]
- **Viibryd (/downloads/Drugs/DrugSafety/UCM241524.pdf)** (vilazodone hydrochloride) [3/2015 version]
- **Vimovo (/downloads/Drugs/DrugSafety/UCM213832.pdf)** (esomeprazole magnesium and naproxen) [3/2014 version]
- **Vimpat (/downloads/Drugs/DrugSafety/ucm089816.pdf)** (lacosamide) [2013 version]
- **Viokace (/downloads/Drugs/DrugSafety/UCM296222.pdf)** (pancrelipase) [2012 version]
- **Viramune and Viramune XR (/downloads/Drugs/DrugSafety/ucm089818.pdf)** (nevirapine) [2014 version]
- **Visicol (/downloads/Drugs/DrugSafety/UCM134684.pdf)** (sodium phosphate dybasic anhydrous and sodium phosphate monobasic monohydrate) [2013 version]
- **Vivactil (/downloads/Drugs/DrugSafety/ucm089820.pdf)** (protriptyline hydrochloride) [2007 version]
- **Vivitrol (/downloads/Drugs/DrugSafety/UCM206669.pdf)** (naltrexone) [2013 version]
- **Vogelxo (/downloads/Drugs/DrugSafety/UCM448177.pdf)** (testosterone) gel [5/2015 version]
- **Voltaren (/downloads/Drugs/DrugSafety/ucm089822.pdf)** (diclofenac sodium) [2011 version]
- **Votrient (/downloads/Drugs/DrugSafety/UCM188476.pdf)** (pazopanib hydrochloride) [9/2015 version]
- **Vyvanse (/downloads/Drugs/DrugSafety/ucm089823.pdf)** (lisdexamfetamine dimesylate) [1/2015 version]
- **Wellbutrin (/downloads/Drugs/DrugSafety/ucm089824.pdf)** (bupropion hydrochloride) [2014 version]
- **Wellbutrin SR (/downloads/Drugs/DrugSafety/ucm089826.pdf)** (bupropion hydrochloride) [2013 version]
- **Wellbutrin XL (/downloads/Drugs/DrugSafety/UCM172744.pdf)** (buproprion hydrochloride) [2011 version]
- **Xarelto (/downloads/Drugs/DrugSafety/UCM280333.pdf)** (rivaroxaban) [6/ 2015 version]
- **Xartemis XR (/downloads/Drugs/DrugSafety/UCM389284.pdf)** (oxycodone hydrochloride and acetaminophen) [3/2015 version]
- **Xeljanz (/downloads/Drugs/DrugSafety/UCM330702.pdf)** (tofacitinib) [3/2014 version]
- **Xenazine (/downloads/Drugs/DrugSafety/ucm089827.pdf)** (tetrabenazine) [6/2015 version]
- **Xeomin (/downloads/Drugs/DrugSafety/UCM222360.pdf)*** (incobotulinumtoxinA) [2011 version]
- **Xiaflex (/downloads/Drugs/DrugSafety/UCM200615.pdf)*** (collagenase clostridium histolyticum) [2013 version]
- **Xolair (/downloads/Drugs/DrugSafety/ucm089829.pdf)*** (omalizumab) [9/2014 version]
- **Xtampza ER (/downloads/Drugs/DrugSafety/UCM497980.pdf)** (oxycodone) [4/2016 version]New!!
- **Xyrem (/downloads/Drugs/DrugSafety/ucm089830.pdf)** (sodium oxybate) [4/2015 version]
- **Yervoy (/downloads/Drugs/DrugSafety/UCM249168.pdf)*** (ipilimumab) [12/2013 version]
- **Zarontin (/downloads/Drugs/DrugSafety/UCM227571.pdf)** (ethosuximide) [2012 version]
- **Zegerid (/downloads/Drugs/DrugSafety/UCM328349.pdf)** (omeprazole and sodium bicarbonate) [2014 version]
- **Zelboraf (/downloads/Drugs/DrugSafety/UCM268332.pdf)** (vemurafenib) [11/2014 version]
- **Zenpep (/downloads/Drugs/DrugSafety/UCM180714.pdf)** (pancrelipase) [2014 version]

- Methylin (methylphenidate)
  - **chewable tablets (/downloads/Drugs/DrugSafety/ucm088639.pdf)** [2013 version]
  - **oral solution (/downloads/Drugs/DrugSafety/ucm088640.pdf)** [2013 version]
- **Metoclopramide Oral Solution (/downloads/Drugs/DrugSafety/UCM244086.pdf)** [2009 version]
- **Metozolv ODT (/downloads/Drugs/DrugSafety/UCM187064.pdf)** (metoclopramide hydrochloride) [2011 version]
- **Mifeprex (/downloads/Drugs/DrugSafety/ucm088643.pdf)** (mifepristone) [2016 version]
- **Mircera (/downloads/Drugs/DrugSafety/ucm088644.pdf)*** (methoxy polyethylene glycol-epoetin beta) [10/2014 version]
- **Mitigare (/downloads/Drugs/DrugSafety/UCM417495.pdf)**(Colchicine) [9/2014 version]
- **Zerit (/downloads/Drugs/DrugSafety/UCM238427.pdf)** (stavudine) [2011 version]
- **Ziagen (/downloads/Drugs/DrugSafety/UCM224556.pdf)** (abacavir sulfate) [9/2015 version]
- **Zipsor (/downloads/Drugs/DrugSafety/UCM243355.pdf)** (diclofenac potassium) [2009 version]
- **Zohydro ER (/downloads/Drugs/DrugSafety/UCM374009.pdf)** (hydrocodone bitartrate) [2014 version]
- **Zoloft (/downloads/Drugs/DrugSafety/ucm089832.pdf)** (sertraline hydrochloride) [2012 version]
- **Zolpidem (/downloads/Drugs/DrugSafety/ucm089833.pdf)** (zolpidem tartrate) [2008 version]
- **Zolpimist (/downloads/Drugs/DrugSafety/UCM143465.pdf)** (zolpidem tartrate) [2008 version]
- **Zonegran (/downloads/Drugs/DrugSafety/UCM152828.pdf)** (zonisamide) [4/2016 version] UPDATED
- **Zontivity (/downloads/Drugs/DrugSafety/UCM447698.pdf)** (vorapaxar) [2013 version]
- **Zortress (/downloads/Drugs/DrugSafety/UCM209840.pdf)** (everolimus) [2013 version]
- **Zorvolex (/downloads/Drugs/DrugSafety/UCM372061.pdf)** (diclofenac) [2013 version]
- **Zubsolv (/downloads/Drugs/DrugSafety/UCM362203.pdf)** (buprenorphine and naloxone) [2013 version]
- **Zyban (/downloads/Drugs/DrugSafety/ucm089835.pdf)** (bupropion hydrochloride) [3/2014 version]
- **Zyprexa (/downloads/Drugs/DrugSafety/UCM134700.pdf)** (olanzapine) [2013 version]
- **Zyprexa Relprevv (/downloads/Drugs/DrugSafety/UCM194579.pdf)** (olanzapine) [2012 version]

Related Information

- **Medication Guides for Certain Prescription Products (/ForConsumers/ConsumerUpdates/ucm107825.htm)** [ARCHIVED]
  Consumer Update article
- **Guidance for Industry: Medication Guides - Distribution Requirements and Inclusion in REMS (PDF - 91KB) (/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM244570.pdf)**
  Final version (11/17/2011)
- **Questions and Answers on Draft Guidance for Industry: Medication Guides - Distribution Requirements and Inclusion in REMS (/Drugs/DrugSafety/ucm248459.htm)**
  3/29/2011
- **Public Hearing on Use of Medication Guides to Distribute Drug Risk Information to Patients June 12-13, 2007 (/Drugs/DrugSafety/ucm172845.htm)**

Drug Supply Chain Integrity

Resources for You

- Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)
- DailyMed (http://dailymed.nlm.nih.gov/dailymed/about.cfm)
- Distribution of Medication Guides (video) (/Drugs/ResourcesForYou/HealthProfessionals/ucm324171.htm)
- Approved Risk Evaluation and Mitigation Strategies (REMS) (http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm)

EXHIBIT “H”

Medication Guide

Cordarone® ′KOR-DU-RŌN Tablets
(amiodarone HCl)

Read the Medication Guide that comes with Cordarone Tablets before you start taking them and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about Cordarone Tablets?
Cordarone Tablets can cause serious side effects that can lead to death including:

- **lung damage**
- **liver damage**
- **worse heartbeat problems**
- **thyroid problems**

Call your doctor or get medical help right away if you have any symptoms such as the following:

- shortness of breath, wheezing, or any other trouble breathing; coughing, chest pain, or spitting up of blood
- nausea or vomiting; passing brown or dark-colored urine; feel more tired than usual; your skin and whites of your eyes get yellow; or have stomach pain
- heart pounding, skipping a beat, beating very fast or very slowly; feel light-headed or faint
- weakness, weight loss or weight gain, heat or cold intolerance, hair thinning, sweating, changes in your menses, swelling of your neck (goiter), nervousness, irritability, restlessness, decreased concentration, depression in the elderly, or tremor.

Because of these possible side effects, Cordarone Tablets should only be used in adults with life-threatening heartbeat problems called ventricular arrhythmias, for which other treatments did not work or were not tolerated.

Cordarone Tablets can cause other serious side effects. See **"What are the possible or reasonably likely side effects of Cordarone Tablets?"** for more information.

If you get serious side effects during treatment with Cordarone Tablets you may need to stop Cordarone Tablets, have your dose changed, or get medical treatment. Talk with your doctor before you stop taking Cordarone Tablets.

You may still have side effects after stopping Cordarone Tablets because the medicine stays in your body months after treatment is stopped.

Tell all your healthcare providers that you take or took Cordarone Tablets. This information is very important for other medical treatments or surgeries you may have.

What are Cordarone Tablets?
Cordarone is a medicine used in adults to treat life-threatening heartbeat problems called ventricular arrhythmias, for which other treatment did not work or was not tolerated. Cordarone Tablets have not been shown to help people with life-threatening heartbeat problems live longer. Treatment with Cordarone Tablets should be started in a hospital to monitor your condition. You should have regular check-ups, blood tests, chest x-rays, and eye exams before and during treatment with Cordarone Tablets to check for serious side effects.

Cordarone Tablets have not been studied in children.

Who should not take Cordarone Tablets?
Do not take Cordarone Tablets if you:

- **have certain heart conditions** (heart block, very slow heart rate, or slow heart rate with dizziness or lightheadedness)
- **have an allergy to amiodarone, iodine, or any of the other ingredients in Cordarone Tablets.** See the end of this Medication Guide for a complete list of ingredients in Cordarone Tablets.

What should I tell my doctor before starting Cordarone Tablets?
Tell your doctor about all of your medical conditions including if you:

- **have lung or breathing problems**
- **have liver problems**
- **have or had thyroid problems**
- **have blood pressure problems**
- **are pregnant or planning to become pregnant.** Cordarone can harm your unborn baby. Cordarone can stay in your body for months after treatment is stopped. Therefore, talk with your doctor before you plan to get pregnant.
- **are breastfeeding.** Cordarone passes into your milk and can harm your baby. You should not breast feed while taking Cordarone. Also, Cordarone can stay in your body for months after treatment is stopped.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. Cordarone Tablets and certain other medicines can interact with each other causing serious side effects. Sometimes the dose of Cordarone Tablets or other medicines must be changed when they are used together. Especially, tell your doctor if you are taking:

- antibiotic medicines used to treat infections
- depression medicines
- blood thinner medicines
- HIV or AIDS medicines
- cimetidine (Tagamet®), a medicine for stomach ulcers or indigestion

- loratadine (for example: Claritin®, Alavert®), a medicine for allergy symptoms
- seizure medicines
- diabetes medicines
- cyclosporine, an immunosuppressive medicine
- dextromethorphan, a cough medicine
- medicines for your heart, circulation, or blood pressure
- water pills (diuretics)
- high cholesterol or bile medicines
- narcotic pain medicines
- St. John's Wort

Know the medicines you take. Keep a list of them with you at all times and show it to your doctor and pharmacist each time you get a new medicine. Do not take any new medicines while you are taking Cordarone Tablets unless you have talked with your doctor.

How should I take Cordarone Tablets?

- **Take Cordarone Tablets exactly as prescribed by your doctor.**
- The dose of Cordarone Tablets you take has been specially chosen for you by your doctor and may change during treatment. Keep taking your medicine until your doctor tells you to stop. Do not stop taking it because you feel better. Your condition may get worse. Talk with your doctor if you have side effects.
- Your doctor will tell you to take your dose of Cordarone Tablets with or without meals. Make sure you take Cordarone Tablets the same way each time.
- **Do not drink grapefruit juice during treatment with Cordarone Tablets.** Grapefruit juice affects how Cordarone is absorbed in the stomach.
- Taking too many Cordarone Tablets can be dangerous. If you take too many Cordarone Tablets, call your doctor or go to the nearest hospital right away. You may need medical care right away.
- If you miss a dose, do not take a double dose to make up for the dose you missed. Continue with your next regularly scheduled dose.

What should I avoid while taking Cordarone Tablets?

- **Do not drink grapefruit juice during treatment with Cordarone Tablets.** Grapefruit juice affects how Cordarone is absorbed in the stomach.
- **Avoid exposing your skin to the sun or sun lamps.** Cordarone Tablets can cause a photosensitive reaction. Wear sun-block cream or protective clothing when out in the sun.
- **Avoid pregnancy during treatment with Cordarone Tablets.** Cordarone can harm your unborn baby.
- **Do not breastfeed while taking Cordarone Tablets.** Cordarone passes into your milk and can harm your baby.

What are the possible or reasonably likely side effects of Cordarone Tablets?
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Cordarone Tablets can cause serious side effects that lead to death including lung damage, liver damage, worse heartbeat problems, and thyroid problems. See **"What is the most important information I should know about Cordarone Tablets?"**

Some other serious side effects of Cordarone Tablets include:

- **vision problems that may lead to permanent blindness.** You should have regular eye exams before and during treatment with Cordarone Tablets. Call your doctor if you have blurred vision, see halos, or your eyes become sensitive to light.
- **nerve problems.** Cordarone Tablets can cause a feeling of "pins and needles" or numbness in the hands, legs, or feet, muscle weakness, uncontrolled movements, poor coordination, and trouble walking.
- **thyroid problems.** Cordarone Tablets can cause thyroid problems, including low thyroid function or overactive thyroid function. Your doctor may arrange regular blood tests to check your thyroid function during treatment with Cordarone. Call your doctor if you have weakness, weight loss or weight gain, heat or cold intolerance, hair thinning, sweating, changes in your menses, swelling of your neck (goiter), nervousness, irritability, restlessness, decreased concentration, depression in the elderly, or tremor.
- **skin problems.** Cordarone Tablets can cause your skin to be more sensitive to the sun or to turn a bluish-gray color. In most patients, skin color slowly returns to normal after stopping Cordarone Tablets. In some patients, skin color does not return to normal.

Other side effects of Cordarone Tablets include nausea, vomiting, constipation, and loss of appetite.

Call your doctor about any side effect that bothers you.

These are not all the side effects with Cordarone Tablets. For more information, ask your doctor or pharmacist.

How should I store Cordarone Tablets?

- Store Cordarone Tablets at room temperature. Protect from light. Keep Cordarone Tablets in a tightly closed container.
- Safely dispose of Cordarone Tablets that are out-of-date or no longer needed.
- **Keep Cordarone Tablets and all medicines out of the reach of children.**

General information about Cordarone Tablets
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Cordarone Tablets for a condition for which it was not prescribed. Do not share Cordarone with other people, even if they have the same symptoms that you have. It may harm them.

If you have any questions or concerns about Cordarone Tablets, ask your doctor or healthcare provider. This Medication Guide summarizes the most important information about Cordarone Tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Cordarone Tablets that was written for healthcare professionals.

This product's Medication Guide may have been updated. For current Medication Guide, please visit www.pfizer.com.

What are the ingredients in Cordarone Tablets?
Active Ingredient: amiodarone HCl

Inactive Ingredients: colloidal silicon dioxide, lactose, magnesium stearate, povidone, starch, and FD&C Red 40.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by Sanofi Winthrop Industrie
1, rue de la Vierge
33440 Ambares, France

Distributed by
Wyeth Pharmaceuticals Inc
A subsidiary of Pfizer Inc, Philadelphia, PA 19101

LAB-0565-1.0
Revised October 2011

EXHIBIT “I”

CFR - Code of Federal Regulations Title 21

The information on this page is current as of April 1 2015.

For the most up-to-date version of CFR Title 21, go to the Electronic Code of Federal Regulations (eCFR).[6]

[Code of Federal Regulations]
[Title 21, Volume 4]
[Revised as of April 1, 2015]
[CITE: 21CFR208.24]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER C--DRUGS: GENERAL

PART 208 -- MEDICATION GUIDES FOR PRESCRIPTION DRUG PRODUCTS

Subpart B--General Requirements for a Medication Guide

Sec. 208.24 Distributing and dispensing a Medication Guide.

(a) The manufacturer of a drug product for which a Medication Guide is required under this part shall obtain FDA approval of the Medication Guide before the Medication Guide may be distributed.

(b) Each manufacturer who ships a container of drug product for which a Medication Guide is required under this part is responsible for ensuring that Medication Guides are available for distribution to patients by either:

(1) Providing Medication Guides in sufficient numbers to distributors, packers, or authorized dispensers to permit the authorized dispenser to provide a Medication Guide to each patient receiving a prescription for the drug product; or

(2) Providing the means to produce Medication Guides in sufficient numbers to distributors, packers, or authorized dispensers to permit the authorized dispenser to provide a Medication Guide to each patient receiving a prescription for the drug product.

(c) Each distributor or packer that receives Medication Guides, or the means to produce Medication Guides, from a manufacturer under paragraph (b) of this section shall provide those Medication Guides, or the means to produce Medication Guides, to each authorized dispenser to whom it ships a container of drug product.

(d) The label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner.

(e) Each authorized dispenser of a prescription drug product for which a Medication Guide is required under this part shall, when the product is dispensed to a patient (or to a patient's agent), provide a Medication Guide directly to each patient (or to the patient's agent) unless an exemption applies under 208.26.

(f) An authorized dispenser or wholesaler is not subject to section 510 of the Federal Food, Drug, and Cosmetic Act, which requires the registration of producers of drugs and the listing of drugs in commercial distribution, solely because of an act performed by the authorized dispenser or wholesaler under this part.

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8. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/ucm135680.htm

Page Last Updated: 08/21/2015

Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

Accessibility Contact FDA Careers FDA Basics FOIA No FEAR Act Site Map Transparency Website Policies

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)
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For Government For Press

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U.S. Department of **Health & Human Services**

Links on this page:

EXHIBIT “J”

NCPA®

the NATIONAL COMMUNITY PHARMACISTS ASSOCIATION

THE VOICE OF COMMUNITY PHARMACY

Use of Medication Guides to Distribute Drug Risk Information to Patients June 13, 2007

Colleen Brennan, RPh
Bryan Ziegler, PharmD, MBA

National Community Pharmacists Association

- Founded in 1898 NCPA represents the pharmacist owners, managers, and employees of more than 24,000 independent community pharmacies across the United States
- The nation's independent pharmacies dispense nearly half of the nation's retail prescription medicines
- We share the FDA’s interest in making sure that patients utilize medication appropriately and have access to information so they can make informed healthcare decisions

FDA Questions for Pharmacy

- How are pharmacists informed a MedGuide needs to be dispensed?
- How do pharmacists receive MedGuides from manufacturers (e.g., in what format)?
- Challenges in supply…what changes should be made to the Medication Guide program to address these challenges?
- Implementation of electronic distribution (e.g., e-mailed to patients)
- Are MedGuides a valuable tool in counseling patients about drugs with serious risks?
- Should the information be combined or simplified into fewer communication vehicles or do they contain unique information?
- What process improvements could be made to ensure that patients receive appropriate drug risk information at the pharmacy?
- Class MedGuides…advantages/disadvantages

MedGuides in Today's Community Pharmacies

- Required on 60 plus drugs
  - when the NDCs for all distributors' products are tallied, a total of around 9100 require MedGuides….First DataBank current data
- Variable and inconsistent methods to obtain
- Variable readability, length (up to 30 plus pages)
- PDF only
- Patients receive multiple and duplicative types of information (CMI, PPI, PIS)
- Variable methods to inform pharmacist of MedGuide requirement
- Required on new prescription and refills

Medication Guide Distribution

- Inconsistency in how pharmacist is informed to distribute
  - Trade organizations and magazines
  - Computer vendor
  - Drug companies (drug representative)
  - Email notification
  - Colleagues

MedGuides From Manufacturers

- Often manufacturers do not provide pharmacists with MedGuides
- No uniform way to acquire from manufacturers - mechanisms include
  - Tear-off pads with reorder form
  - Attached to the prescription product container (either separate from or buried in prescribing info…but only 1 copy/container)
  - Toll free 800 numbers for pharmacies to order hard copies

Challenges Complying With MedGuide Regulation

- Difficulty incorporating into pharmacy workflow
  - Storage
  - Stopping work flow to download from website
  - Printing on separate printer
- Getting accurate information to distribute….knowing which drugs are required (sheer number of drugs)
- Too much paper for patients
- Pharmacies incur the cost of printing (cost shift to pharmacy from manufacturer)

Electronic Distribution of MedGuides

- Pharmacies would require a good web based program that would interface with the pharmacy management system
- Email is not always practical (retail environment very different)
  - Many patients don't use email
  - Would require an opt-in from patient
  - Increased work flow interruption (beyond normal MedGuide issues due to internet access, changing pharmacy management systems to access patient's email)
- Good or bad depending on where you live
  - Rural internet access a concern
- Electronic format for *manual* printing may cause inconsistent delivery
- If implemented still need availability of *paper* MedGuides

Class MedGuides

- Advantages:
  - Gives an overview about the dangers of all medications in that class and a snapshot of how they work
  - Coalition of manufacturers worked well for NSAIDs and antidepressants giving pharmacy a single point of ordering and consistency in the class MedGuide itself
- Disadvantages:
  - Not all medications are created equal
  - Blanket statements about a class of medications do NOT necessarily mean that it will apply to the one medication from that class that a patient is on and can in some ways, create needless fear in a patient

MedGuide Value as a Patient Counseling Tool

- Difficult to utilize
  - Length and readability
    - Well designed studies on MedGuide effectiveness are needed
    - Reading comprehension of patient versus technical level of the MedGuide
- Patients and caregivers often don't understand them and are sometimes frightened of the "risk" only information
- Patient confusion due to duplicative information (PPI, PIS, CMI)
- MedGuides for refills should be up to pharmacist discretion

NCPA MedGuide Recommendations

- Enforce current FDA MedGuide regulation holding manufacturers accountable for providing:
  - "Medication Guides in sufficient numbers, or the means to produce Medication Guides in sufficient numbers, to permit the authorized dispenser to provide a Medication Guide to each patient who receives a prescription for the drug product"

NCPA MedGuide Recommendations

- Revise MedGuide regulation to:
  - Mandate that product manufacturers create electronic, user friendly, product class MedGuides with access on a NDC based database as well as providing *paper* MedGuides
  - Allow incorporation of MedGuides into pharmacy software…caveat: could increase costs of printing because the printers would use a lot more paper
  - Combine branded and generic MedGuides as one document

NCPA MedGuide Recommendations

- Standard message system needed to inform pharmacists
  - Flag drugs – either on container or through pharmacy management system
- Standard ordering system needed for pharmacy
  - FDA ask manufacturers of like MedGuides to form coalition again
  - Allow CMI vendors to provide MedGuides to pharmacy along with CMI

NCPA MedGuide Recommendations

- MedGuides need to be available in *both* hard copy and electronically so that the pharmacies/software vendors can implement the most appropriate version for their workflow/operations
- Formatting standards must be changed so pharmacies can print MedGuides even if they cannot download a PDF file
- Manufacturers *must* bear the direct and indirect costs of distribution &/or printing by pharmacies

MedGuide Printing Cost Estimates

Current Printing Requirements

Average Pages in MedGuide (now)	8		Total Pages	2,240,000,000
Total # of Rx requiring MedGuide/yr	280,000,000 *		Cost/page	$0.0401 **
Total # of Pages printed/year	2,240,000,000		Total AnnualCost	$89,920,000

Possible Printing Requirements (if MedGuides 2 pages in length)

Average Pages in MedGuide	2		Total Pages	560,000,000
Total # of Rx requiring MedGuide/yr	280,000,000 *		Cost/page	$0.0401 **
Total # of Pages printed/year	560,000,000		Total Annual Cost	$22,480,000

*Note: Estimated 7% of prescriptions filled require MedGuide.

**Note: Cost/page calculation includes toner cost + paper cost + administrative cost

***Note: Cost calculations do not factor in any expense for warranty or cost of an additional printer.

MedGuide Printing Cost Estimates

Prices Used in Cost Estimate Calculations

Item	Max Yield (pages)	Price	Source	Cost/page
Lexmark T640 Toner Cartridge	21,000	$352	OfficeDepot.com	$0.0168
Paper (5000 sheets/case)		$50	Staples.com	$0.01
Administrative Cost*				$0.0134
			Estimated Cost/Page	**$0.0401**

Other Prices to Consider (Not Included in Cost Estimate Calculations)

Lexmark T640DN Printer**	$1,100	Staples.com	
Warranty	$130-220	Annually	Lexmark

*Administrative cost applied to cover the expense incurred during acquisition, delivery, and storage of supplies used in printing of Medication Guides. Administrative cost is estimated at 50% of cost/page of toner and paper.
**Lexmark is primary brand printer used in retail pharmacy. Customer service representative identified the T640 model as most common used in pharmacies.

NCPA®

the NATIONAL COMMUNITY PHARMACISTS ASSOCIATION

THE VOICE OF COMMUNITY PHARMACY

JS 44 (Rev. 12/12)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. *(SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)*

I. (a) PLAINTIFFS
Bobbye Jean Cooper

(b) County of Residence of First Listed Plaintiff Travis County
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorneys *(Firm Name, Address, and Telephone Number)*
The Snapka Law Firm; P.O. Drawer 23017, Corpus Christi, TX 78403; (361) 888-7676; Fax (361) 884-8545

DEFENDANTS
Wyeth Pharmaceuticals, Inc.

County of Residence of First Listed Defendant Morris County
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

Attorneys *(If Known)*

II. BASIS OF JURISDICTION *(Place an "X" in One Box Only)*

- ❒ 1 U.S. Government Plaintiff
- ❒ 3 Federal Question *(U.S. Government Not a Party)*
- ❒ 2 U.S. Government Defendant
- ❒ 4 Diversity *(Indicate Citizenship of Parties in Item III)*

III. CITIZENSHIP OF PRINCIPAL PARTIES *(Place an "X" in One Box for Plaintiff and One Box for Defendant)*
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☒ 1	❒ 1	Incorporated *or* Principal Place of Business In This State	❒ 4	❒ 4
Citizen of Another State	❒ 2	❒ 2	Incorporated *and* Principal Place of Business In Another State	❒ 5	☒ 5
Citizen or Subject of a Foreign Country	❒ 3	❒ 3	Foreign Nation	❒ 6	❒ 6

IV. NATURE OF SUIT *(Place an "X" in One Box Only)*

CONTRACT
- ❒ 110 Insurance
- ❒ 120 Marine
- ❒ 130 Miller Act
- ❒ 140 Negotiable Instrument
- ❒ 150 Recovery of Overpayment & Enforcement of Judgment
- ❒ 151 Medicare Act
- ❒ 152 Recovery of Defaulted Student Loans (Excludes Veterans)
- ❒ 153 Recovery of Overpayment of Veteran's Benefits
- ❒ 160 Stockholders' Suits
- ❒ 190 Other Contract
- ❒ 195 Contract Product Liability
- ❒ 196 Franchise

REAL PROPERTY
- ❒ 210 Land Condemnation
- ❒ 220 Foreclosure
- ❒ 230 Rent Lease & Ejectment
- ❒ 240 Torts to Land
- ❒ 245 Tort Product Liability
- ❒ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ❒ 310 Airplane
- ❒ 315 Airplane Product Liability
- ❒ 320 Assault, Libel & Slander
- ❒ 330 Federal Employers' Liability
- ❒ 340 Marine
- ❒ 345 Marine Product Liability
- ❒ 350 Motor Vehicle
- ❒ 355 Motor Vehicle Product Liability
- ❒ 360 Other Personal Injury
- ❒ 362 Personal Injury - Medical Malpractice

PERSONAL INJURY
- ☒ 365 Personal Injury - Product Liability
- ❒ 367 Health Care/ Pharmaceutical Personal Injury Product Liability
- ❒ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ❒ 370 Other Fraud
- ❒ 371 Truth in Lending
- ❒ 380 Other Personal Property Damage
- ❒ 385 Property Damage Product Liability

CIVIL RIGHTS
- ❒ 440 Other Civil Rights
- ❒ 441 Voting
- ❒ 442 Employment
- ❒ 443 Housing/ Accommodations
- ❒ 445 Amer. w/Disabilities - Employment
- ❒ 446 Amer. w/Disabilities - Other
- ❒ 448 Education

PRISONER PETITIONS

Habeas Corpus:
- ❒ 463 Alien Detainee
- ❒ 510 Motions to Vacate Sentence
- ❒ 530 General
- ❒ 535 Death Penalty

Other:
- ❒ 540 Mandamus & Other
- ❒ 550 Civil Rights
- ❒ 555 Prison Condition
- ❒ 560 Civil Detainee - Conditions of Confinement

FORFEITURE/PENALTY
- ❒ 625 Drug Related Seizure of Property 21 USC 881
- ❒ 690 Other

LABOR
- ❒ 710 Fair Labor Standards Act
- ❒ 720 Labor/Management Relations
- ❒ 740 Railway Labor Act
- ❒ 751 Family and Medical Leave Act
- ❒ 790 Other Labor Litigation
- ❒ 791 Employee Retirement Income Security Act

IMMIGRATION
- ❒ 462 Naturalization Application
- ❒ 465 Other Immigration Actions

BANKRUPTCY
- ❒ 422 Appeal 28 USC 158
- ❒ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ❒ 820 Copyrights
- ❒ 830 Patent
- ❒ 840 Trademark

SOCIAL SECURITY
- ❒ 861 HIA (1395ff)
- ❒ 862 Black Lung (923)
- ❒ 863 DIWC/DIWW (405(g))
- ❒ 864 SSID Title XVI
- ❒ 865 RSI (405(g))

FEDERAL TAX SUITS
- ❒ 870 Taxes (U.S. Plaintiff or Defendant)
- ❒ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ❒ 375 False Claims Act
- ❒ 400 State Reapportionment
- ❒ 410 Antitrust
- ❒ 430 Banks and Banking
- ❒ 450 Commerce
- ❒ 460 Deportation
- ❒ 470 Racketeer Influenced and Corrupt Organizations
- ❒ 480 Consumer Credit
- ❒ 490 Cable/Sat TV
- ❒ 850 Securities/Commodities/ Exchange
- ❒ 890 Other Statutory Actions
- ❒ 891 Agricultural Acts
- ❒ 893 Environmental Matters
- ❒ 895 Freedom of Information Act
- ❒ 896 Arbitration
- ❒ 899 Administrative Procedure Act/Review or Appeal of Agency Decision
- ❒ 950 Constitutionality of State Statutes

V. ORIGIN *(Place an "X" in One Box Only)*

☒ 1 Original Proceeding ❒ 2 Removed from State Court ❒ 3 Remanded from Appellate Court ❒ 4 Reinstated or Reopened ❒ 5 Transferred from Another District *(specify)* ❒ 6 Multidistrict Litigation

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing ***(Do not cite jurisdictional statutes unless diversity)***:
28 U.S.C. Section 1391

Brief description of cause:
Personal injury as a result of using Defendants' amiodarone product

VII. REQUESTED IN COMPLAINT:

❒ CHECK IF THIS IS A **CLASS ACTION** UNDER RULE 23, F.R.Cv.P.

DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ☒ Yes ❒ No

VIII. RELATED CASE(S) IF ANY
(See instructions):

JUDGE Lee Yeakel DOCKET NUMBER 1:15-cv-822; 1:14-cv-549

DATE 05/19/2016

SIGNATURE OF ATTORNEY OF RECORD /s/ Kathryn Snapka

FOR OFFICE USE ONLY

RECEIPT # AMOUNT APPLYING IFP JUDGE MAG. JUDGE

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS 44

Authority For Civil Cover Sheet

The JS 44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently, a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

I.(a) **Plaintiffs-Defendants.** Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title.

(b) **County of Residence.** For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) **Attorneys.** Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

II. **Jurisdiction.** The basis of jurisdiction is set forth under Rule 8(a), F.R.Cv.P., which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.
United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here.
United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.
Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.
Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below**; NOTE: federal question actions take precedence over diversity cases.**)

III. **Residence (citizenship) of Principal Parties.** This section of the JS 44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

IV. **Nature of Suit.** Place an "X" in the appropriate box. If the nature of suit cannot be determined, be sure the cause of action, in Section VI below, is sufficient to enable the deputy clerk or the statistical clerk(s) in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive.

V. **Origin.** Place an "X" in one of the six boxes.
Original Proceedings. (1) Cases which originate in the United States district courts.
Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C., Section 1441. When the petition for removal is granted, check this box.
Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.
Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.
Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.
Multidistrict Litigation. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407. When this box is checked, do not check (5) above.

VI. **Cause of Action.** Report the civil statute directly related to the cause of action and give a brief description of the cause. **Do not cite jurisdictional statutes unless diversity.** Example: U.S. Civil Statute: 47 USC 553 Brief Description: Unauthorized reception of cable service

VII. **Requested in Complaint.** Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.
Demand. In this space enter the actual dollar amount being demanded or indicate other demand, such as a preliminary injunction.
Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

VIII. **Related Cases.** This section of the JS 44 is used to reference related pending cases, if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

Date and Attorney Signature. Date and sign the civil cover sheet.