



Memorandum

Date: May 31, 2007

To: Pediatric Subcommittee of the Oncologic Drugs Advisory Committee Members, Consultants, and Guests

From: Karen D. Weiss, M.D. *Karen Weiss*
Deputy Director, Office of Oncology Drug Products, CDER, FDA

Subject: FDA Background Package for June 27, 2007 Meeting

Thank you for agreeing to participate in the subcommittee session scheduled for June 27, 2007. This one day meeting will cover two major topics. The morning session is devoted to a review and discussion of the impact of the Best Pharmaceuticals for Children Act (BPCA) on the field of pediatric oncology. The exclusivity provisions (6 months marketing exclusivity in return for conduct of pediatric studies consistent with the terms of a pediatric Written Request) have been in place for 10 years – first with the 1997 passage of the FDA Modernization Act (FDAMA), and subsequently with the passage of the 2002 BPCA legislation. BPCA sunsets this year; discussions are underway in Congress regarding its renewal. This is an opportune time to review the dozen or so 'on-patent' oncology drugs that have been studied in children with cancer as a result of FDAMA and BPCA. Following a summary of BPCA and a presentation of the studies and data resulting in exclusivity, we will seek your input on ways to:

- identify in a timely manner drugs that have the potential to benefit children with cancer and
- develop Written Requests that will result in studies and data that provide the most useful information.

The afternoon's session focuses on 13-*cis*-retinoic acid, a drug NICHHD recently added to their priority list for 'off patent drugs'. Following a brief review of the BPCA off patent process and summary of the existing information on the use of 13-*cis*-retinoic acid in patients with high risk neuroblastoma, we will seek input on

- elements to include in a Written Request for 13-*cis*-retinoic acid in neuroblastoma.

As always, we appreciate your time and commitment and look forward to an informative meeting on June 27th.

**Pediatric Oncology Subcommittee
of the Oncologic Drugs Advisory Committee (ODAC)
June 27, 2007**

FDA Briefing Document

**TABLE OF CONTENTS
Session I: BPCA & Oncology Experience**

1. BPCA On-Patent Process (for products with market exclusivity)

a. 2002 Best Pharmaceuticals for Children Act (BPCA) – Section 4 and 5, pages 4-7 (also available at: <http://www.fda.gov/cder/pediatric/PL107-109.pdf>) [17p]

b. BPCA Slide Presentations

(1) L. Mathis, M.D., Associate Director, Pediatric and Maternal Health Staff, Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER), FDA. Presentation from October 2005 Pediatric Subcommittee of the Oncologic Drugs Advisory Committee Meeting. “Pediatric Drug Development Initiatives” [20 slides] (also available at: http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4185S1_04_FDA-Mathis_files/frame.htm)

(2) K. Weiss, M.D., Deputy Director, Office of Oncology Drug Products, OND, CDER, FDA. Presentation from May 2006 Accelerating Anticancer Agent Development and Validation Workshop. “Regulatory Issues in Pediatric Cancer” [21 slides]

2. Table of Oncology Products with BPCA Exclusivity [1p]

3. Executive Summaries of Medical and Clinical Pharmacology Reviews for Oncology Products with BPCA Exclusivity

Section 9 of the BPCA (item 1, page 8) mandates that within 180 days after the submission of a pediatric study report, a summary of the medical and clinical pharmacology reviews of pediatric studies conducted will be made publicly available. The executive summaries included here (source: <http://www.fda.gov/cder/pediatric/Summaryreview.htm>) lists nine oncologic drugs for which summaries are available. Summaries are not publicly available for products for which pediatric study reports were submitted prior to July 2002 (i.e., busulfan and vinorelbine).

a. **Carboplatin (Paraplatin®)**

(1) Clinical Review (12p)

(also available at: http://www.fda.gov/cder/foi/esum/2004/19880se8-019_Paraplatin_clin_BPCA.pdf)

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- (2) Clinical Pharmacology (2p)
(also available at: http://www.fda.gov/cder/foi/esum/2004/19880se8-019_Paraplatin_exec_summ_BPCA.pdf)

- b. **Clofarabine (Clolar®)**
 - (1) Clinical (4p)
(also available at: http://www.fda.gov/cder/foi/esum/2005/21673_Clolar_Clinical_Execsum_BPCA.pdf)
 - (2) Clinical Pharmacology (7p)
(also available at: http://www.fda.gov/cder/foi/esum/2005/21673_Clolar_Pharm_Biopharm_BPCA.pdf)

- c. **Fludarabine (Fludara®)**
 - (1) Clinical Review (4p)
(also available at: <http://www.fda.gov/cder/foi/esum/2003/20038se8-028BPCAltr.pdf>)
 - (2) Clinical Pharmacology (3p)
(also available at: <http://www.fda.gov/cder/foi/esum/2003/20038SE8028BPCAltr.pdf>)

- d. **Gemcitabine (Gemzar®)**
 - (1) Clinical Review (4p)
(also available at: http://www.fda.gov/cder/foi/esum/2006/020509s033_Gemcitabine_Medical_BPCA.pdf)

- e. **Imatinib (Gleevec®)**
 - (1) Clinical Review (7p)
(also available at: http://www.fda.gov/cder/foi/esum/2006/021588s016_Imatinib_Mesylyate_Clinical_BPCA.pdf)
 - (2) Clinical Pharmacology (4p)
(also available at: http://www.fda.gov/cder/foi/esum/2006/021588s016_Imatinib_meslyate_ClinPharm_BPCA.pdf)

- f. **Irinotecan (Camptosar®)**
 - (1) Clinical Review (6p)
(also available at: http://www.fda.gov/cder/foi/esum/2004/20571se8-021_Camptosar_Med_Off_BPCA_ltr.pdf)
 - (2) Clinical Pharmacology (8p)
(also available at: http://www.fda.gov/cder/foi/esum/2004/20571se8-021_Camptosar_Pharm_biopharm_BPCA.pdf)

- g. **Oxaliplatin (Eloxatin®)**
 - (1) Clinical Review (4p)
(also available at: http://www.fda.gov/cder/foi/esum/2007/021492s008_Oxaliplatin_Clinical_BPCA.pdf)

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FDA Briefing Document

(2) Clinical Pharmacology (5p)

(also available at:

http://www.fda.gov/cder/foi/esum/2007/021492S8s008_Oxaliplatin_ClinPharm-BioPharm_BPCA.pdf)

h. Temozolomide (Temodar®)

(1) Clinical Review (6p)

(also available at: <http://www.fda.gov/cder/foi/esum/2003/21029se8005.pdf>)

(2) Clinical Pharmacology (3p)

(also available at: <http://www.fda.gov/cder/foi/esum/2003/21029se8-005rev2.pdf>)

i. Topotecan (Hycamtin®)

(1) Clinical Review (3p)

(also available at: <http://www.fda.gov/cder/foi/esum/2003/20671se8-010BPCA.pdf>)

(2) Clinical Pharmacology (3p)

(also available at: <http://www.fda.gov/cder/foi/esum/2003/20671s010.pdf>)

4. Table of Safety Reporting (1 year review) for Oncology Products with BPCA Exclusivity

Section 17 of the BPCA (item 1, pages 15-16) mandates that products granted pediatric exclusivity will have a post exclusivity review and report on adverse events which will be presented to the FDA's Pediatric Advisory Committee. The table included here (condensed from <http://www.fda.gov/oc/opt/pediatricsafety.html>) lists nine oncologic drugs granted pediatric exclusivity, the date exclusivity was granted, the date presented to the Pediatric Advisory Committee, and the Committee recommendations. Each product name is also linked to the various Pediatric Advisory Committee documents. Oxaliplatin and imatinib are not listed because they are less than 1 year from the date that pediatric exclusivity was granted, the threshold for safety review and consideration by the Pediatric Advisory Committee. [1p]

One Hundred Seventh Congress
of the
United States of America

AT THE FIRST SESSION

*Begun and held at the City of Washington on Wednesday,
the third day of January, two thousand and one*

An Act

To amend the Federal Food, Drug, and Cosmetic Act to improve the safety and efficacy of pharmaceuticals for children.

*Be it enacted by the Senate and House of Representatives of
the United States of America in Congress assembled,*

SECTION 1. SHORT TITLE.

This Act may be cited as the “Best Pharmaceuticals for Children Act”.

SEC. 2. PEDIATRIC STUDIES OF ALREADY-MARKETED DRUGS.

Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) is amended—

- (1) by striking subsection (b); and
- (2) in subsection (c)—

(A) by inserting after “the Secretary” the following: “determines that information relating to the use of an approved drug in the pediatric population may produce health benefits in that population and”; and

(B) by striking “concerning a drug identified in the list described in subsection (b)”.

SEC. 3. RESEARCH FUND FOR THE STUDY OF DRUGS.

Part B of title IV of the Public Health Service Act (42 U.S.C. 284 et seq.) is amended—

- (1) by redesignating the second section 409C, relating to clinical research (42 U.S.C. 284k), as section 409G;
- (2) by redesignating the second section 409D, relating to enhancement awards (42 U.S.C. 284l), as section 409H; and
- (3) by adding at the end the following:

“SEC. 409I. PROGRAM FOR PEDIATRIC STUDIES OF DRUGS.

“(a) LIST OF DRUGS FOR WHICH PEDIATRIC STUDIES ARE NEEDED.—

“(1) IN GENERAL.—Not later than one year after the date of enactment of this section, the Secretary, acting through the Director of the National Institutes of Health and in consultation with the Commissioner of Food and Drugs and experts in pediatric research, shall develop, prioritize, and publish an annual list of approved drugs for which—

“(A)(i) there is an approved application under section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j));

“(ii) there is a submitted application that could be approved under the criteria of section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j));

“(iii) there is no patent protection or market exclusivity protection under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.); or

“(iv) there is a referral for inclusion on the list under section 505A(d)(4)(C) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(d)(4)(C)); and

“(B) in the case of a drug referred to in clause (i), (ii), or (iii) of subparagraph (A), additional studies are needed to assess the safety and effectiveness of the use of the drug in the pediatric population.

“(2) CONSIDERATION OF AVAILABLE INFORMATION.—In developing and prioritizing the list under paragraph (1), the Secretary shall consider, for each drug on the list—

“(A) the availability of information concerning the safe and effective use of the drug in the pediatric population;

“(B) whether additional information is needed;

“(C) whether new pediatric studies concerning the drug may produce health benefits in the pediatric population; and

“(D) whether reformulation of the drug is necessary.

“(b) CONTRACTS FOR PEDIATRIC STUDIES.—The Secretary shall award contracts to entities that have the expertise to conduct pediatric clinical trials (including qualified universities, hospitals, laboratories, contract research organizations, federally funded programs such as pediatric pharmacology research units, other public or private institutions, or individuals) to enable the entities to conduct pediatric studies concerning one or more drugs identified in the list described in subsection (a).

“(c) PROCESS FOR CONTRACTS AND LABELING CHANGES.—

“(1) WRITTEN REQUEST TO HOLDERS OF APPROVED APPLICATIONS FOR DRUGS LACKING EXCLUSIVITY.—The Commissioner of Food and Drugs, in consultation with the Director of the National Institutes of Health, may issue a written request (which shall include a timeframe for negotiations for an agreement) for pediatric studies concerning a drug identified in the list described in subsection (a)(1)(A) (except clause (iv)) to all holders of an approved application for the drug under section 505 of the Federal Food, Drug, and Cosmetic Act. Such a written request shall be made in a manner equivalent to the manner in which a written request is made under subsection (a) or (b) of section 505A of the Federal Food, Drug, and Cosmetic Act, including with respect to information provided on the pediatric studies to be conducted pursuant to the request.

“(2) REQUESTS FOR CONTRACT PROPOSALS.—If the Commissioner of Food and Drugs does not receive a response to a written request issued under paragraph (1) within 30 days of the date on which a request was issued, or if a referral described in subsection (a)(1)(A)(iv) is made, the Secretary, acting through the Director of the National Institutes of Health and in consultation with the Commissioner of Food and Drugs, shall publish a request for contract proposals to conduct the pediatric studies described in the written request.

“(3) DISQUALIFICATION.—A holder that receives a first right of refusal shall not be entitled to respond to a request for contract proposals under paragraph (2).

“(4) GUIDANCE.—Not later than 270 days after the date of enactment of this section, the Commissioner of Food and

Drugs shall promulgate guidance to establish the process for the submission of responses to written requests under paragraph (1).

“(5) CONTRACTS.—A contract under this section may be awarded only if a proposal for the contract is submitted to the Secretary in such form and manner, and containing such agreements, assurances, and information as the Secretary determines to be necessary to carry out this section.

“(6) REPORTING OF STUDIES.—

“(A) IN GENERAL.—On completion of a pediatric study in accordance with a contract awarded under this section, a report concerning the study shall be submitted to the Director of the National Institutes of Health and the Commissioner of Food and Drugs. The report shall include all data generated in connection with the study.

“(B) AVAILABILITY OF REPORTS.—Each report submitted under subparagraph (A) shall be considered to be in the public domain (subject to section 505A(d)(4)(D) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(d)(4)(D)) and shall be assigned a docket number by the Commissioner of Food and Drugs. An interested person may submit written comments concerning such pediatric studies to the Commissioner of Food and Drugs, and the written comments shall become part of the docket file with respect to each of the drugs.

“(C) ACTION BY COMMISSIONER.—The Commissioner of Food and Drugs shall take appropriate action in response to the reports submitted under subparagraph (A) in accordance with paragraph (7).

“(7) REQUESTS FOR LABELING CHANGE.—During the 180-day period after the date on which a report is submitted under paragraph (6)(A), the Commissioner of Food and Drugs shall—

“(A) review the report and such other data as are available concerning the safe and effective use in the pediatric population of the drug studied;

“(B) negotiate with the holders of approved applications for the drug studied for any labeling changes that the Commissioner of Food and Drugs determines to be appropriate and requests the holders to make; and

“(C)(i) place in the public docket file a copy of the report and of any requested labeling changes; and

“(ii) publish in the Federal Register a summary of the report and a copy of any requested labeling changes.

“(8) DISPUTE RESOLUTION.—

“(A) REFERRAL TO PEDIATRIC ADVISORY SUBCOMMITTEE OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE.—If, not later than the end of the 180-day period specified in paragraph (7), the holder of an approved application for the drug involved does not agree to any labeling change requested by the Commissioner of Food and Drugs under that paragraph, the Commissioner of Food and Drugs shall refer the request to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee.

“(B) ACTION BY THE PEDIATRIC ADVISORY SUBCOMMITTEE OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE.—Not later than 90 days after receiving a referral

under subparagraph (A), the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee shall—

“(i) review the available information on the safe and effective use of the drug in the pediatric population, including study reports submitted under this section; and

“(ii) make a recommendation to the Commissioner of Food and Drugs as to appropriate labeling changes, if any.

“(9) FDA DETERMINATION.—Not later than 30 days after receiving a recommendation from the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee under paragraph (8)(B)(ii) with respect to a drug, the Commissioner of Food and Drugs shall consider the recommendation and, if appropriate, make a request to the holders of approved applications for the drug to make any labeling change that the Commissioner of Food and Drugs determines to be appropriate.

“(10) FAILURE TO AGREE.—If a holder of an approved application for a drug, within 30 days after receiving a request to make a labeling change under paragraph (9), does not agree to make a requested labeling change, the Commissioner may deem the drug to be misbranded under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.).

“(11) NO EFFECT ON AUTHORITY.—Nothing in this subsection limits the authority of the United States to bring an enforcement action under the Federal Food, Drug, and Cosmetic Act when a drug lacks appropriate pediatric labeling. Neither course of action (the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee process or an enforcement action referred to in the preceding sentence) shall preclude, delay, or serve as the basis to stay the other course of action.

“(12) RECOMMENDATION FOR FORMULATION CHANGES.—If a pediatric study completed under public contract indicates that a formulation change is necessary and the Secretary agrees, the Secretary shall send a nonbinding letter of recommendation regarding that change to each holder of an approved application.

“(d) AUTHORIZATION OF APPROPRIATIONS.—

“(1) IN GENERAL.—There are authorized to be appropriated to carry out this section—

“(A) \$200,000,000 for fiscal year 2002; and

“(B) such sums as are necessary for each of the five succeeding fiscal years.

“(2) AVAILABILITY.—Any amount appropriated under paragraph (1) shall remain available to carry out this section until expended.”.

SEC. 4. WRITTEN REQUEST TO HOLDERS OF APPROVED APPLICATIONS FOR DRUGS THAT HAVE MARKET EXCLUSIVITY.

Section 505A(d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(d)) is amended by adding at the end the following:

“(4) WRITTEN REQUEST TO HOLDERS OF APPROVED APPLICATIONS FOR DRUGS THAT HAVE MARKET EXCLUSIVITY.—

“(A) REQUEST AND RESPONSE.—If the Secretary makes a written request for pediatric studies (including neonates, as appropriate) under subsection (c) to the holder of an application approved under section 505(b)(1), the holder, not later than 180 days after receiving the written request, shall respond to the Secretary as to the intention of the holder to act on the request by—

“(i) indicating when the pediatric studies will be initiated, if the holder agrees to the request; or

“(ii) indicating that the holder does not agree to the request.

“(B) NO AGREEMENT TO REQUEST.—

“(i) REFERRAL.—If the holder does not agree to a written request within the time period specified in subparagraph (A), and if the Secretary determines that there is a continuing need for information relating to the use of the drug in the pediatric population (including neonates, as appropriate), the Secretary shall refer the drug to the Foundation for the National Institutes of Health established under section 499 of the Public Health Service Act (42 U.S.C. 290b) (referred to in this paragraph as the ‘Foundation’) for the conduct of the pediatric studies described in the written request.

“(ii) PUBLIC NOTICE.—The Secretary shall give public notice of the name of the drug, the name of the manufacturer, and the indications to be studied made in a referral under clause (i).

“(C) LACK OF FUNDS.—On referral of a drug under subparagraph (B)(i), the Foundation shall issue a proposal to award a grant to conduct the requested studies unless the Foundation certifies to the Secretary, within a time-frame that the Secretary determines is appropriate through guidance, that the Foundation does not have funds available under section 499(j)(9)(B)(i) to conduct the requested studies. If the Foundation so certifies, the Secretary shall refer the drug for inclusion on the list established under section 409I of the Public Health Service Act for the conduct of the studies.

“(D) EFFECT OF SUBSECTION.—Nothing in this subsection (including with respect to referrals from the Secretary to the Foundation) alters or amends section 301(j) of this Act or section 552 of title 5 or section 1905 of title 18, United States Code.

“(E) NO REQUIREMENT TO REFER.—Nothing in this subsection shall be construed to require that every declined written request shall be referred to the Foundation.

“(F) WRITTEN REQUESTS UNDER SUBSECTION (b).—For drugs under subsection (b) for which written requests have not been accepted, if the Secretary determines that there is a continuing need for information relating to the use of the drug in the pediatric population (including neonates, as appropriate), the Secretary shall issue a written request under subsection (c) after the date of approval of the drug.”.

SEC. 5. TIMELY LABELING CHANGES FOR DRUGS GRANTED EXCLUSIVITY; DRUG FEES.

(a) **ELIMINATION OF USER FEE WAIVER FOR PEDIATRIC SUPPLEMENTS.**—Section 736(a)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379h(a)(1)) is amended—

(1) by striking subparagraph (F); and

(2) by redesignating subparagraph (G) as subparagraph (F).

(b) **LABELING CHANGES.**—

(1) **DEFINITION OF PRIORITY SUPPLEMENT.**—Section 201 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321) is amended by adding at the end the following:

“(kk) **PRIORITY SUPPLEMENT.**—The term ‘priority supplement’ means a drug application referred to in section 101(4) of the Food and Drug Administration Modernization Act of 1997 (111 Stat. 2298).”.

(2) **TREATMENT AS PRIORITY SUPPLEMENTS.**—Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) is amended by adding at the end the following:

“(l) **LABELING SUPPLEMENTS.**—

“(1) **PRIORITY STATUS FOR PEDIATRIC SUPPLEMENTS.**—Any supplement to an application under section 505 proposing a labeling change pursuant to a report on a pediatric study under this section—

“(A) shall be considered to be a priority supplement; and

“(B) shall be subject to the performance goals established by the Commissioner for priority drugs.

“(2) **DISPUTE RESOLUTION.**—

“(A) **REQUEST FOR LABELING CHANGE AND FAILURE TO AGREE.**—If the Commissioner determines that an application with respect to which a pediatric study is conducted under this section is approvable and that the only open issue for final action on the application is the reaching of an agreement between the sponsor of the application and the Commissioner on appropriate changes to the labeling for the drug that is the subject of the application, not later than 180 days after the date of submission of the application—

“(i) the Commissioner shall request that the sponsor of the application make any labeling change that the Commissioner determines to be appropriate; and

“(ii) if the sponsor of the application does not agree to make a labeling change requested by the Commissioner, the Commissioner shall refer the matter to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee.

“(B) **ACTION BY THE PEDIATRIC ADVISORY SUBCOMMITTEE OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE.**—Not later than 90 days after receiving a referral under subparagraph (A)(ii), the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee shall—

“(i) review the pediatric study reports; and

“(ii) make a recommendation to the Commissioner concerning appropriate labeling changes, if any.

“(C) CONSIDERATION OF RECOMMENDATIONS.—The Commissioner shall consider the recommendations of the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee and, if appropriate, not later than 30 days after receiving the recommendation, make a request to the sponsor of the application to make any labeling change that the Commissioner determines to be appropriate.

“(D) MISBRANDING.—If the sponsor of the application, within 30 days after receiving a request under subparagraph (C), does not agree to make a labeling change requested by the Commissioner, the Commissioner may deem the drug that is the subject of the application to be misbranded.

“(E) NO EFFECT ON AUTHORITY.—Nothing in this subsection limits the authority of the United States to bring an enforcement action under this Act when a drug lacks appropriate pediatric labeling. Neither course of action (the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee process or an enforcement action referred to in the preceding sentence) shall preclude, delay, or serve as the basis to stay the other course of action.”.

SEC. 6. OFFICE OF PEDIATRIC THERAPEUTICS.

(a) ESTABLISHMENT.—The Secretary of Health and Human Services shall establish an Office of Pediatric Therapeutics within the Food and Drug Administration.

(b) DUTIES.—The Office of Pediatric Therapeutics shall be responsible for coordination and facilitation of all activities of the Food and Drug Administration that may have any effect on a pediatric population or the practice of pediatrics or may in any other way involve pediatric issues.

(c) STAFF.—The staff of the Office of Pediatric Therapeutics shall coordinate with employees of the Department of Health and Human Services who exercise responsibilities relating to pediatric therapeutics and shall include—

(1) one or more additional individuals with expertise concerning ethical issues presented by the conduct of clinical research in the pediatric population; and

(2) one or more additional individuals with expertise in pediatrics as may be necessary to perform the activities described in subsection (b).

SEC. 7. NEONATES.

Section 505A(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(g)) is amended by inserting “(including neonates in appropriate cases)” after “pediatric age groups”.

SEC. 8. SUNSET.

Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) is amended by striking subsection (j) and inserting the following:

“(j) SUNSET.—A drug may not receive any 6-month period under subsection (a) or (c) unless—

“(1) on or before October 1, 2007, the Secretary makes a written request for pediatric studies of the drug;

“(2) on or before October 1, 2007, an application for the drug is accepted for filing under section 505(b); and

“(3) all requirements of this section are met.”.

SEC. 9. DISSEMINATION OF PEDIATRIC INFORMATION.

Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) (as amended by section 5(b)(2)) is amended by adding at the end the following:

“(m) DISSEMINATION OF PEDIATRIC INFORMATION.—

“(1) IN GENERAL.—Not later than 180 days after the date of submission of a report on a pediatric study under this section, the Commissioner shall make available to the public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted for the supplement, including by publication in the Federal Register.

“(2) EFFECT OF SUBSECTION.—Nothing in this subsection alters or amends section 301(j) of this Act or section 552 of title 5 or section 1905 of title 18, United States Code.”.

SEC. 10. CLARIFICATION OF INTERACTION OF PEDIATRIC EXCLUSIVITY UNDER SECTION 505A OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT AND 180-DAY EXCLUSIVITY AWARDED TO AN APPLICANT FOR APPROVAL OF A DRUG UNDER SECTION 505(j) OF THAT ACT.

Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) (as amended by section 9) is amended by adding at the end the following:

“(n) CLARIFICATION OF INTERACTION OF MARKET EXCLUSIVITY UNDER THIS SECTION AND MARKET EXCLUSIVITY AWARDED TO AN APPLICANT FOR APPROVAL OF A DRUG UNDER SECTION 505(j).—If a 180-day period under section 505(j)(5)(B)(iv) overlaps with a 6-month exclusivity period under this section, so that the applicant for approval of a drug under section 505(j) entitled to the 180-day period under that section loses a portion of the 180-day period to which the applicant is entitled for the drug, the 180-day period shall be extended from—

“(1) the date on which the 180-day period would have expired by the number of days of the overlap, if the 180-day period would, but for the application of this subsection, expire after the 6-month exclusivity period; or

“(2) the date on which the 6-month exclusivity period expires, by the number of days of the overlap if the 180-day period would, but for the application of this subsection, expire during the six-month exclusivity period.”.

SEC. 11. PROMPT APPROVAL OF DRUGS UNDER SECTION 505(j) WHEN PEDIATRIC INFORMATION IS ADDED TO LABELING.

(a) IN GENERAL.—Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) (as amended by section 10) is amended by adding at the end the following:

“(o) PROMPT APPROVAL OF DRUGS UNDER SECTION 505(j) WHEN PEDIATRIC INFORMATION IS ADDED TO LABELING.—

“(1) GENERAL RULE.—A drug for which an application has been submitted or approved under section 505(j) shall not be considered ineligible for approval under that section or misbranded under section 502 on the basis that the labeling of the drug omits a pediatric indication or any other aspect of labeling pertaining to pediatric use when the omitted indication

or other aspect is protected by patent or by exclusivity under clause (iii) or (iv) of section 505(j)(5)(D).

“(2) LABELING.—Notwithstanding clauses (iii) and (iv) of section 505(j)(5)(D), the Secretary may require that the labeling of a drug approved under section 505(j) that omits a pediatric indication or other aspect of labeling as described in paragraph (1) include—

“(A) a statement that, because of marketing exclusivity for a manufacturer—

“(i) the drug is not labeled for pediatric use; or

“(ii) in the case of a drug for which there is an additional pediatric use not referred to in paragraph (1), the drug is not labeled for the pediatric use under paragraph (1); and

“(B) a statement of any appropriate pediatric contraindications, warnings, or precautions that the Secretary considers necessary.

“(3) PRESERVATION OF PEDIATRIC EXCLUSIVITY AND OTHER PROVISIONS.—This subsection does not affect—

“(A) the availability or scope of exclusivity under this section;

“(B) the availability or scope of exclusivity under section 505 for pediatric formulations;

“(C) the question of the eligibility for approval of any application under section 505(j) that omits any other conditions of approval entitled to exclusivity under clause (iii) or (iv) of section 505(j)(5)(D); or

“(D) except as expressly provided in paragraphs (1) and (2), the operation of section 505.”

(b) EFFECTIVE DATE.—The amendment made by subsection (a) takes effect on the date of enactment of this Act, including with respect to applications under section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)) that are approved or pending on that date.

SEC. 12. STUDY CONCERNING RESEARCH INVOLVING CHILDREN.

(a) CONTRACT WITH INSTITUTE OF MEDICINE.—The Secretary of Health and Human Services shall enter into a contract with the Institute of Medicine for—

(1) the conduct, in accordance with subsection (b), of a review of—

(A) Federal regulations in effect on the date of the enactment of this Act relating to research involving children;

(B) federally prepared or supported reports relating to research involving children; and

(C) federally supported evidence-based research involving children; and

(2) the submission to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives, not later than two years after the date of enactment of this Act, of a report concerning the review conducted under paragraph (1) that includes recommendations on best practices relating to research involving children.

(b) AREAS OF REVIEW.—In conducting the review under subsection (a)(1), the Institute of Medicine shall consider the following:

(1) The written and oral process of obtaining and defining “assent”, “permission” and “informed consent” with respect to child clinical research participants and the parents, guardians, and the individuals who may serve as the legally authorized representatives of such children (as defined in subpart A of part 46 of title 45, Code of Federal Regulations).

(2) The expectations and comprehension of child research participants and the parents, guardians, or legally authorized representatives of such children, for the direct benefits and risks of the child’s research involvement, particularly in terms of research versus therapeutic treatment.

(3) The definition of “minimal risk” with respect to a healthy child or a child with an illness.

(4) The appropriateness of the regulations applicable to children of differing ages and maturity levels, including regulations relating to legal status.

(5) Whether payment (financial or otherwise) may be provided to a child or his or her parent, guardian, or legally authorized representative for the participation of the child in research, and if so, the amount and type of payment that may be made.

(6) Compliance with the regulations referred to in subsection (a)(1)(A), the monitoring of such compliance (including the role of institutional review boards), and the enforcement actions taken for violations of such regulations.

(7) The unique roles and responsibilities of institutional review boards in reviewing research involving children, including composition of membership on institutional review boards.

(c) REQUIREMENTS OF EXPERTISE.—The Institute of Medicine shall conduct the review under subsection (a)(1) and make recommendations under subsection (a)(2) in conjunction with experts in pediatric medicine, pediatric research, and the ethical conduct of research involving children.

SEC. 13. FOUNDATION FOR THE NATIONAL INSTITUTES OF HEALTH.

Section 499 of the Public Health Service Act (42 U.S.C. 290b) is amended—

(1) in subsection (b), by inserting “(including collection of funds for pediatric pharmacologic research)” after “mission”;

(2) in subsection (c)(1)—

(A) by redesignating subparagraph (C) as subparagraph (D); and

(B) by inserting after subparagraph (B) the following:

“(C) A program to collect funds for pediatric pharmacologic research and studies listed by the Secretary pursuant to section 409I(a)(1)(A) of this Act and referred under section 505A(d)(4)(C) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(d)(4)(C)).”;

(3) in subsection (d)—

(A) in paragraph (1)—

(i) in subparagraph (B)—

(I) in clause (ii), by striking “and” at the end;

(II) in clause (iii), by striking the period and inserting “; and”;

(III) by adding at the end the following:

“(iv) the Commissioner of Food and Drugs.”; and

(ii) by striking subparagraph (C) and inserting the following:

“(C) The ex officio members of the Board under subparagraph (B) shall appoint to the Board individuals from among a list of candidates to be provided by the National Academy of Science. Such appointed members shall include—

“(i) representatives of the general biomedical field;

“(ii) representatives of experts in pediatric medicine and research;

“(iii) representatives of the general biobehavioral field, which may include experts in biomedical ethics; and

“(iv) representatives of the general public, which may include representatives of affected industries.”; and

(B) in paragraph (2), by realigning the margin of subparagraph (B) to align with subparagraph (A);

(4) in subsection (k)(9)—

(A) by striking “The Foundation” and inserting the following:

“(A) IN GENERAL.—The Foundation”; and

(B) by adding at the end the following:

“(B) GIFTS, GRANTS, AND OTHER DONATIONS.—

“(i) IN GENERAL.—Gifts, grants, and other donations to the Foundation may be designated for pediatric research and studies on drugs, and funds so designated shall be used solely for grants for research and studies under subsection (c)(1)(C).

“(ii) OTHER GIFTS.—Other gifts, grants, or donations received by the Foundation and not described in clause (i) may also be used to support such pediatric research and studies.

“(iii) REPORT.—The recipient of a grant for research and studies shall agree to provide the Director of the National Institutes of Health and the Commissioner of Food and Drugs, at the conclusion of the research and studies—

“(I) a report describing the results of the research and studies; and

“(II) all data generated in connection with the research and studies.

“(iv) ACTION BY THE COMMISSIONER OF FOOD AND DRUGS.—The Commissioner of Food and Drugs shall take appropriate action in response to a report received under clause (iii) in accordance with paragraphs (7) through (12) of section 4091(c), including negotiating with the holders of approved applications for the drugs studied for any labeling changes that the Commissioner determines to be appropriate and requests the holders to make.

“(C) APPLICABILITY.—Subparagraph (A) does not apply to the program described in subsection (c)(1)(C).”;

(5) by redesignating subsections (f) through (m) as subsections (e) through (l), respectively;

(6) in subsection (h)(11) (as so redesignated), by striking “solicit” and inserting “solicit,”; and

(7) in paragraphs (1) and (2) of subsection (j) (as so redesignated), by striking “(including those developed under subsection (d)(2)(B)(i)(II))” each place it appears.

SEC. 14. PEDIATRIC PHARMACOLOGY ADVISORY COMMITTEE.

(a) **IN GENERAL.**—The Secretary of Health and Human Services shall, under section 222 of the Public Health Service Act (42 U.S.C. 217a), convene and consult an advisory committee on pediatric pharmacology (referred to in this section as the “advisory committee”).

(b) **PURPOSE.**—

(1) **IN GENERAL.**—The advisory committee shall advise and make recommendations to the Secretary, through the Commissioner of Food and Drugs and in consultation with the Director of the National Institutes of Health, on matters relating to pediatric pharmacology.

(2) **MATTERS INCLUDED.**—The matters referred to in paragraph (1) include—

(A) pediatric research conducted under sections 351, 409I, and 499 of the Public Health Service Act and sections 501, 502, 505, and 505A of the Federal Food, Drug, and Cosmetic Act;

(B) identification of research priorities related to pediatric pharmacology and the need for additional treatments of specific pediatric diseases or conditions; and

(C) the ethics, design, and analysis of clinical trials related to pediatric pharmacology.

(c) **COMPOSITION.**—The advisory committee shall include representatives of pediatric health organizations, pediatric researchers, relevant patient and patient-family organizations, and other experts selected by the Secretary.

SEC. 15. PEDIATRIC SUBCOMMITTEE OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE.

(a) **CLARIFICATION OF AUTHORITIES.**—

(1) **IN GENERAL.**—The Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (referred to in this section as the “Subcommittee”), in carrying out the mission of reviewing and evaluating the data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of pediatric cancers, shall—

(A) evaluate and, to the extent practicable, prioritize new and emerging therapeutic alternatives available to treat pediatric cancer;

(B) provide recommendations and guidance to help ensure that children with cancer have timely access to the most promising new cancer therapies; and

(C) advise on ways to improve consistency in the availability of new therapeutic agents.

(2) **MEMBERSHIP.**—

(A) **IN GENERAL.**—The Secretary shall appoint not more than 11 voting members to the Pediatric Subcommittee from the membership of the Pediatric Pharmacology Advisory Committee and the Oncologic Drugs Advisory Committee.

(B) **REQUEST FOR PARTICIPATION.**—The Subcommittee shall request participation of the following members in

the scientific and ethical consideration of topics of pediatric cancer, as necessary:

(i) At least two pediatric oncology specialists from the National Cancer Institute.

(ii) At least four pediatric oncology specialists from—

(I) the Children’s Oncology Group;

(II) other pediatric experts with an established history of conducting clinical trials in children; or

(III) consortia sponsored by the National Cancer Institute, such as the Pediatric Brain Tumor Consortium, the New Approaches to Neuroblastoma Therapy or other pediatric oncology consortia.

(iii) At least two representatives of the pediatric cancer patient and patient-family community.

(iv) One representative of the nursing community.

(v) At least one statistician.

(vi) At least one representative of the pharmaceutical industry.

(b) PRE-CLINICAL MODELS TO EVALUATE PROMISING PEDIATRIC CANCER THERAPIES.—Section 413 of the Public Health Service Act (42 U.S.C. 285a–2) is amended by adding at the end the following:

“(c) PRE-CLINICAL MODELS TO EVALUATE PROMISING PEDIATRIC CANCER THERAPIES.—

“(1) EXPANSION AND COORDINATION OF ACTIVITIES.—The Director of the National Cancer Institute shall expand, intensify, and coordinate the activities of the Institute with respect to research on the development of preclinical models to evaluate which therapies are likely to be effective for treating pediatric cancer.

“(2) COORDINATION WITH OTHER INSTITUTES.—The Director of the Institute shall coordinate the activities under paragraph (1) with similar activities conducted by other national research institutes and agencies of the National Institutes of Health to the extent that those Institutes and agencies have responsibilities that are related to pediatric cancer.”

(c) CLARIFICATION OF AVAILABILITY OF INVESTIGATIONAL NEW DRUGS FOR PEDIATRIC STUDY AND USE.—

(1) AMENDMENT OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.—Section 505(i)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)(1)) is amended—

(A) in subparagraph (B), by striking “and” at the end;

(B) in subparagraph (C), by striking the period at the end and inserting “; and”; and

(C) by adding at the end the following:

“(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) AMENDMENT OF THE PUBLIC HEALTH SERVICE ACT.—Section 402(j)(3)(A) of the Public Health Service Act (42 U.S.C. 282(j)(3)(A)) is amended in the first sentence—

(A) by striking “trial sites, and” and inserting “trial sites,”; and

(B) by striking “in the trial,” and inserting “in the trial, and a description of whether, and through what procedure, the manufacturer or sponsor of the investigation of a new drug will respond to requests for protocol exception, with appropriate safeguards, for single-patient and expanded protocol use of the new drug, particularly in children.”.

(d) REPORT.—Not later than January 31, 2003, the Secretary of Health and Human Services, acting through the Commissioner of Food and Drugs and in consultation with the Director of the National Institutes of Health, shall submit to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives a report on patient access to new therapeutic agents for pediatric cancer, including access to single patient use of new therapeutic agents.

SEC. 16. REPORT ON PEDIATRIC EXCLUSIVITY PROGRAM.

Not later than October 1, 2006, the Comptroller General of the United States, in consultation with the Secretary of Health and Human Services, shall submit to Congress a report that addresses the following issues, using publicly available data or data otherwise available to the Government that may be used and disclosed under applicable law:

(1) The effectiveness of section 505A of the Federal Food, Drug, and Cosmetic Act and section 409I of the Public Health Service Act (as added by this Act) in ensuring that medicines used by children are tested and properly labeled, including—

(A) the number and importance of drugs for children that are being tested as a result of this legislation and the importance for children, health care providers, parents, and others of labeling changes made as a result of such testing;

(B) the number and importance of drugs for children that are not being tested for their use notwithstanding the provisions of this legislation, and possible reasons for the lack of testing; and

(C) the number of drugs for which testing is being done, exclusivity granted, and labeling changes required, including the date pediatric exclusivity is granted and the date labeling changes are made and which labeling changes required the use of the dispute resolution process established pursuant to the amendments made by this Act, together with a description of the outcomes of such process, including a description of the disputes and the recommendations of the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee.

(2) The economic impact of section 505A of the Federal Food, Drug, and Cosmetic Act and section 409I of the Public Health Service Act (as added by this Act), including an estimate of—

(A) the costs to taxpayers in the form of higher expenditures by medicaid and other Government programs;

(B) sales for each drug during the 6-month period for which exclusivity is granted, as attributable to such exclusivity;

(C) costs to consumers and private insurers as a result of any delay in the availability of lower cost generic equivalents of drugs tested and granted exclusivity under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.), and loss of revenue by the generic drug industry and retail pharmacies as a result of any such delay; and

(D) the benefits to the government, to private insurers, and to consumers resulting from decreased health care costs, including—

(i) decreased hospitalizations and fewer medical errors, due to more appropriate and more effective use of medications in children as a result of testing and re-labeling because of the amendments made by this Act;

(ii) direct and indirect benefits associated with fewer physician visits not related to hospitalization;

(iii) benefits to children from missing less time at school and being less affected by chronic illnesses, thereby allowing a better quality of life;

(iv) benefits to consumers from lower health insurance premiums due to lower treatment costs and hospitalization rates; and

(v) benefits to employers from reduced need for employees to care for family members.

(3) The nature and type of studies in children for each drug granted exclusivity under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.), including—

(A) a description of the complexity of the studies;

(B) the number of study sites necessary to obtain appropriate data;

(C) the number of children involved in any clinical studies; and

(D) the estimated cost of each of the studies.

(4) Any recommendations for modifications to the programs established under section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) and section 409I of the Public Health Service Act (as added by section 3) that the Secretary determines to be appropriate, including a detailed rationale for each recommendation.

(5) The increased private and Government-funded pediatric research capability associated with this Act and the amendments made by this Act.

(6) The number of written requests and additional letters of recommendation that the Secretary issues.

(7) The prioritized list of off-patent drugs for which the Secretary issues written requests.

(8)(A) The efforts made by the Secretary to increase the number of studies conducted in the neonate population; and

(B) the results of those efforts, including efforts made to encourage the conduct of appropriate studies in neonates by companies with products that have sufficient safety and other information to make the conduct of studies ethical and safe.

SEC. 17. ADVERSE-EVENT REPORTING.

(a) TOLL-FREE NUMBER IN LABELING.—Not later than one year after the date of the enactment of this Act, the Secretary of Health and Human Services shall promulgate a final rule requiring that

the labeling of each drug for which an application is approved under section 505 of the Federal Food, Drug, and Cosmetic Act (regardless of the date on which approved) include the toll-free number maintained by the Secretary for the purpose of receiving reports of adverse events regarding drugs and a statement that such number is to be used for reporting purposes only, not to receive medical advice. With respect to the final rule:

(1) The rule shall provide for the implementation of such labeling requirement in a manner that the Secretary considers to be most likely to reach the broadest consumer audience.

(2) In promulgating the rule, the Secretary shall seek to minimize the cost of the rule on the pharmacy profession.

(3) The rule shall take effect not later than 60 days after the date on which the rule is promulgated.

(b) DRUGS WITH PEDIATRIC MARKET EXCLUSIVITY.—

(1) IN GENERAL.—During the one year beginning on the date on which a drug receives a period of market exclusivity under 505A of the Federal Food, Drug, and Cosmetic Act, any report of an adverse event regarding the drug that the Secretary of Health and Human Services receives shall be referred to the Office of Pediatric Therapeutics established under section 6 of this Act. In considering the report, the Director of such Office shall provide for the review of the report by the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee, including obtaining any recommendations of such subcommittee regarding whether the Secretary should take action under the Federal Food, Drug, and Cosmetic Act in response to the report.

(2) RULE OF CONSTRUCTION.—Paragraph (1) may not be construed as restricting the authority of the Secretary of Health and Human Services to continue carrying out the activities described in such paragraph regarding a drug after the one-year period described in such paragraph regarding the drug has expired.

SEC. 18. MINORITY CHILDREN AND PEDIATRIC-EXCLUSIVITY PROGRAM.

(a) PROTOCOLS FOR PEDIATRIC STUDIES.—Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) is amended in subsection (d)(2) by inserting after the first sentence the following: “In reaching an agreement regarding written protocols, the Secretary shall take into account adequate representation of children of ethnic and racial minorities.”

(b) STUDY BY GENERAL ACCOUNTING OFFICE.—

(1) IN GENERAL.—The Comptroller General of the United States shall conduct a study for the purpose of determining the following:

(A) The extent to which children of ethnic and racial minorities are adequately represented in studies under section 505A of the Federal Food, Drug, and Cosmetic Act; and to the extent ethnic and racial minorities are not adequately represented, the reasons for such under representation and recommendations to increase such representation.

(B) Whether the Food and Drug Administration has appropriate management systems to monitor the representation of the children of ethnic and racial minorities in such studies.

(C) Whether drugs used to address diseases that disproportionately affect racial and ethnic minorities are being studied for their safety and effectiveness under section 505A of the Federal Food, Drug, and Cosmetic Act.

(2) DATE CERTAIN FOR COMPLETING STUDY.—Not later than January 10, 2003, the Comptroller General shall complete the study required in paragraph (1) and submit to the Congress a report describing the findings of the study.

SEC. 19. TECHNICAL AND CONFORMING AMENDMENTS.

Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) (as amended by sections 2(1), 5(b)(2), 9, 10, 11, and 17) is amended—

(1)(A) by striking “(j)(4)(D)(ii)” each place it appears and inserting “(j)(5)(D)(ii)”;

(B) by striking “(j)(4)(D)” each place it appears and inserting “(j)(5)(D)”;

(C) by striking “505(j)(4)(D)” each place it appears and inserting “505(j)(5)(D)”;

(2) by redesignating subsections (a), (g), (h), (i), (j), (k), (l), (m), (n), and (o) as subsections (b), (a), (g), (h), (n), (m), (i), (j), (k), and (l) respectively;

(3) by moving the subsections so as to appear in alphabetical order;

(4) in paragraphs (1), (2), and (3) of subsection (d), subsection (e), and subsection (m) (as redesignated by paragraph (2)), by striking “subsection (a) or (c)” and inserting “subsection (b) or (c)”;

(5) in subsection (g) (as redesignated by paragraph (2)), by striking “subsection (a) or (b)” and inserting “subsection (b) or (c)”.

Speaker of the House of Representatives.

*Vice President of the United States and
President of the Senate.*

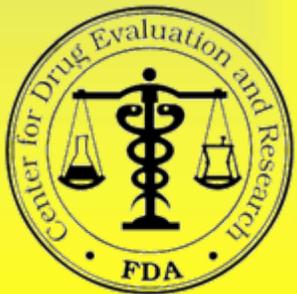
Pediatric Drug Development Initiatives

Lisa Mathis, M.D.

Acting Director

**Division of Pediatric Drug
Development**

October 20, 2005



Pediatric Initiatives

- **Pediatric Research Equity Act, December 3, 2003**
- **Best Pharmaceuticals for Children Act, January 4, 2002**

Both laws are intended to support and encourage drug development in the pediatric population



- **PREA studies are mandatory**
- **BPCA studies are voluntary**

Why Both PREA and BPCA?

- **Distinction between the scope of studies requested under BPCA and required under PREA**
- **PREA specific to indication in submission**
- **BPCA can ask for “off-label” indications**
 - **Sildenafil Citrate (Viagra)**
 - **Pediatric studies required by the Pediatric Rule were waived**
 - **Written Request was issued**

Pediatric Research Equity Act (PREA)

- **Became law December 3, 2003**
- **PREA is the codification of the 1998 Pediatric Rule**
- **Drugs and Biologics affected**
- **Not applicable to drugs with Orphan Designation**

PREA

- One of two laws intended to promote the study of drugs and biologics in pediatric patients
 - Studies prevent pediatric patients from being a “study of one”
- Studies in the pediatric population are **REQUIRED**, but only for the indication that was studied in adults

PREA

- Pediatric Assessment **required** for certain applications unless **waived or deferred**
- Draft Guidance recently issued (9/7/05)

PREA

- **Pediatric Assessment contains**
 - data adequate to assess the safety and effectiveness of the drug or biological product, and
 - data to support dosing and administration for each pediatric subpopulation

PREA

- **Assessment required for applications:**
 - **New ingredient**
 - **New indication**
 - **New dosage form**
 - **New dosing regimen**
 - **New route of administration**

Full Waiver

Waiver granted when:

- Necessary studies impossible or highly impracticable;
- Strong evidence suggests the drug or biologic would be ineffective or unsafe; or
- Product does not represent a meaningful therapeutic benefit over existing therapies **AND** is not likely to be used in a substantial number of pediatric patients

“Substantial Number”

- **PREA does not define substantial number**
- **FDA generally has considered 50,000 patients to be a substantial number**
- **FDA will take into consideration the nature and severity of the condition when making this determination**

Partial Waiver

Partial Waiver is a special waiver for a pediatric age group (i.e. less than 6 months of age) and is granted when:

- The criteria for a full waiver applies to that age group; or**
- Reasonable attempts to produce a pediatric formulation necessary for that age group have failed**

Full and Partial Waiver

Labeling Requirement:

- **If full or partial waiver is granted because there is evidence that the drug or biologic would be ineffective or unsafe, that information must be included in the label**

Deferral

- **A deferral is granted when a pediatric assessment is needed, but permits submission of the pediatric assessment after submission of NDA/BLA**
- **Reasons for deferral**
 - **Drug or biologic is ready for approval in adults;**
 - **Need additional safety data; or**
 - **There is another appropriate reason for deferral**

PREA

- **Not as flexible as BPCA**
- **Indications for required pediatric studies are limited to the indications in a given submission**
 - **An assessment would be waived under PREA in submissions for the treatment of a condition that occurs only in adults**
 - **Prostate, breast cancer**

Best Pharmaceuticals for Children Act (BPCA)

- **Became law January 4, 2002**
- **Renewed authority (FDAMA) to grant six months of marketing exclusivity to Sponsors who conduct and submit studies in response to a Written Request.**
- **Includes an additional mechanism for obtaining information for the use of off-patent drugs in pediatric patients**

PREA and BPCA: Togetherness



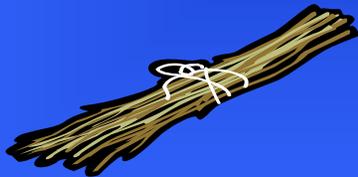
Goal

- **The goal of both PREA and BPCA:**
 - **Obtain information from studies about the use of medications in the pediatric population.**
 - **Obtain studies for both common and rare conditions.**
 - **Disseminate information about the safe and efficacious use of medications in children.**

PREA vs. BPCA

PREA

- Studies mandatory
- Required studies only on drug/indication under review
- Studies for orphan indications not required
- Applies to drugs and biologics
- Sunsets October 1, 2007



BPCA

- Studies voluntary
- Studies on entire active moiety
- WR may be issued for orphan indications
- Applies only to drugs
- Sunsets October 1, 2007



To Contact Division of Pediatric Drug Development:

Peds Line: 301-796-2200

Internet: www.fda.gov/cder/pediatric

Email: pdit@cderr.fda.gov

Regulatory Issues in Pediatric Cancer

2006 Accelerating Anticancer Agent
Development & Validation Workshop

Karen D. Weiss, M.D.
Deputy Director, Office of Oncology Drug Products



Pediatric
oncology drug
development



Pediatric Drug
Development

Tragedies (in children) \Rightarrow laws

1902 - Biologics Control Act

- diphtheria antitoxin contaminated with live tetanus bacilli

1938 - Food, Drug and Cosmetic Act

- sulfanilamide

1962 - Amendments

- thalidomide



Early Benchmarks in Pediatric Drug Development

1977 - AAP Committee on Drugs

- Drugs should be studied in children

1979 - Labeling Requirement

- Labeling for pediatric use of a drug for an indication approved for adults must be based on substantial evidence derived from adequate and well-controlled studies, unless the requirement is waived.
 - Result – few studies, no useful labeling
-

Later Benchmarks

- # 1994 – ‘extrapolation’ of efficacy
 - # 1997 - FDAMA/Exclusivity Provision, **voluntary, incentives**
 - # 1998 - Pediatric Studies **required**
 - # 2001- Subpart D
 - Additional Safeguards for Children in Clinical Investigations of FDA-regulated products
 - # 2002- Best Pharmaceuticals for Children (BPCA)
 - # 2003- Pediatric Research Equity (PREA)
-

Best Pharmaceuticals for Children Act (BPCA) 2002

- # Renewed exclusivity process (on patent drugs)
- # Process for off patent drug development
- # Public posting of study results
- # Review and reporting of AE 1 yr after exclusivity
- # Pediatric subcommittee of ODAC
- # Pre-clinical models



Pediatric Exclusivity

Pediatric Exclusivity- an economic incentive to conduct pediatric studies

The incentive-

- ✓ six months of additional marketing exclusivity
 - ✓ attaches to existing patents and/or exclusivity
-

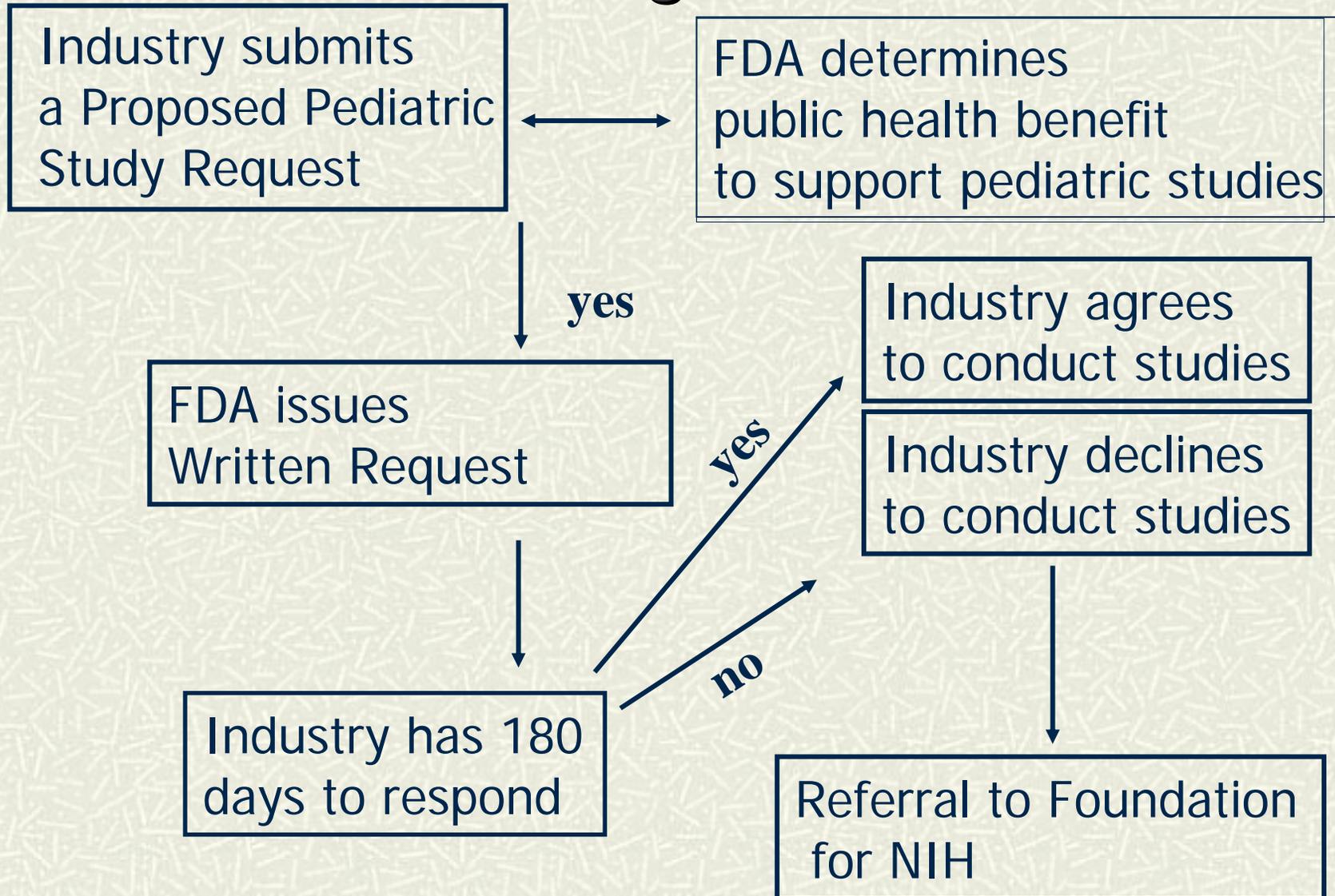
Written Request (WR)

- # A (legal) document sent by the FDA to sponsors requesting studies in the pediatric population
 - # Specifies:
 - ✓ indication
 - ✓ population
 - ✓ type of studies
 - ✓ safety parameters
 - ✓ longer term follow-up
 - ✓ timeframe for response
-

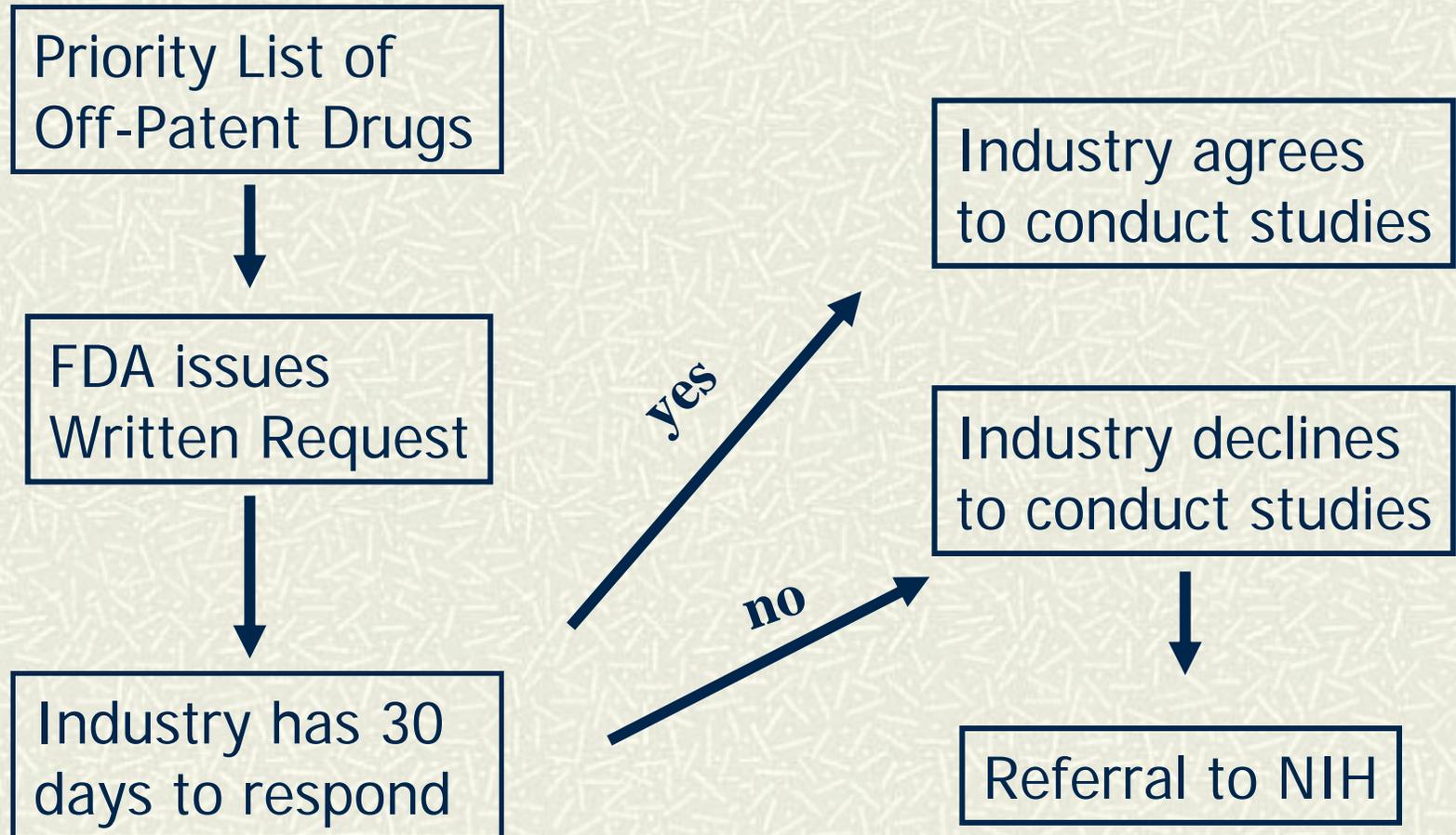
BPCA- Provisions

- Two situations-
 - ✓ FDA issues Written Request to holders of approved application *protected by patent or market exclusivity* → "on-patent"
 - ✓ FDA issues Written Request to holders of approved application *for drugs that have NO patent or market exclusivity protection* → "off-patent"
-

Process for the Study of On-Patent Drugs



Process for the Study of Off-Patent Drugs

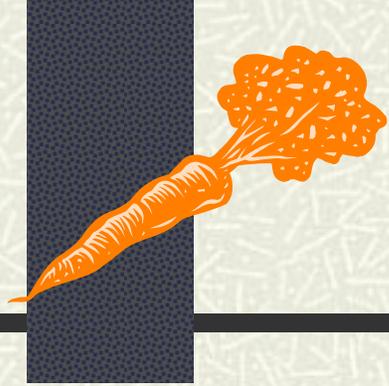


Development of 'the List'

- # The BPCA stipulates that in developing and prioritizing the list, the NIH shall consider;
 - the availability of information concerning the safe and effective use of the drug in the pediatric population
 - whether additional information is needed
 - whether new pediatric studies concerning the drug may produce health benefits in the pediatric population
-

2003 Pediatric Research Equity Act (PREA)

- Codifies 1998 rule - requires study of drugs and biologics in children
 - Presumption: all new indications, dosage forms, routes, etc. for use [in adults] will be studied in children
 - Plan for generating pediatric data
 - At time of the NDA or BLA or supplement
 - Deferred – most common; required post-marketing studies
 - Waived
-



BPCA



PREA

-
- # Voluntary, incentives
 - # Includes orphan indication
 - # Studies on whole moiety, & other indications
 - # Applies only to drugs
 - # Trigger – WR
 - # Results posted regardless of approval
 - # Safety data 1 year later
- # Required, no \$
 - # Orphan indications exempt
 - # Drug/indication under development
 - # Drugs and Biologicals
 - # Trigger – application
 - # Results confidential if not approved
 - # Usual safety reporting
-

Unique issues with pediatric oncology

- # Most pediatric oncology patients are entered into clinical trials
 - “standard of care”
 - # Long history of studying oncology drugs in the pediatric oncology population
 - Infrastructure for dissemination of information about dosing, activity, toxicity
 - # “Off label” but established
-

Unique aspects of pediatric oncology - BPCA

May grant exclusivity:

- after demonstration of response (or lack of), or effect (or lack of) on other surrogates (phase 2)
- After early (phase 1) show unacceptable toxicity that precludes further study

Ideally also provide the information in drug labels

Oncology and BPCA statistics

On Patent:

- # 320 Written Requests Issued (as of 4/30/06)
 - 35 - Oncology Indications
 - 9 – oncology drugs granted exclusivity
 - 6 - label changes

Off Patent

- # 37 off patent drugs listed (as of 4/25/06)
 - 4 – Oncology
 - Vincristine
 - Actinomycin D
 - Daunomycin
 - Methotrexate
-

TABLE 1.—CURRENT STATUS OF DRUGS THAT HAVE BEEN LISTED BY NIH (NICHD) FOR BPCA—Continued

Drug	Indication	Listing	Patent status	Written request/RFP	Clinical trial primary site	Current status and/or clinical trial design
Sodium nitroprusside	Control of blood pressure.	2003	Off-patent	NICHD	Duke and Stanford Universities.	Pharmacokinetics, safety, efficacy by randomized double-blind parallel group study design. Participants are currently being enrolled.
Spironolactone	Diuresis	2003	Off-patent	FDA	NA	Recommend consultation with scientific community concerning diagnosis and treatment of pediatric hypertension and the role of diuretics in treatment.
Vincristine	Cancer	2004	Off-patent	NICHD	NICHD Partnership with NCI/Children's Oncology Group.	Clinical studies being conducted by Children's Oncology Group with National Cancer Institute to better define safety, efficacy, and PK.
Zonisamide*	Partial Seizures	2005	On-patent	FNIH, NICHD.	NA	Written Request referred to FNIH.

Unique aspects of pediatric oncology - PREA

- # Different diseases compared to the majority of adult cancers
 - Anti-tumor indication (in adults) may not exist in pediatric populations
 - Waiver
 - # Other indications – e.g., supportive care more likely to be similar and thus result in required studies under PREA [if not performed under BPCA] or if a biologic
-

Summary

- # Pediatric oncology differs from other pediatric subspecialties
 - Distinctions between diseases in adults and children
 - Long history of clinical research through cooperative groups
- # Legislation (BPCA and PREA) useful tools for studies that otherwise would not be conducted
 - BPCA – on and off patent drugs
 - PREA – biologics, required postmarketing

THE END

Acknowledgements:

Shirley Murphy

Dianne Murphy

Ramzi Dagher

Lisa Mathis

Dotti Pease

Anne Zajicek

**Pediatric Oncology Subcommittee
of the Oncologic Drugs Advisory Committee (ODAC)
June 27, 2007**

**FDA Briefing Document
Session 1: Item 2**

Oncology Products with BPCA Exclusivity

Established	Proprietary	Granted Exclusivity^a	Label Changes^b	Summaries^c	Pediatric AC^e
1. busulfan	Busulfex®	3-12-02	1-13-03	No ^d	Yes: 10-29-03
2. carboplatin	Paraplatin®	4-30-04	N/A	Yes	Yes: 11-18-05
3. clofarabine	Clolar®	7-14-04	12-28-04	Yes	Yes: 3-22-06
4. fludarabine	Fludara ®	4-3-03	8-1-03	Yes	Yes 9-15-04
5. gemcitabine	Gemzar®	1-27-05	4-26-05	Yes	Yes: 11-16-06
6. imatinib	Gleevec®	6-9-06	9-27-06	Yes	No
7. irinotecan	Camptosar®	3-10-04	6-24-04	Yes	Yes 11-18-05
8. oxaliplatin	Eloxatin®	9-27-06	1-10-07	Yes	No
9. temozolomide	Temodar®	11-20-02	3-11-03	Yes	Yes: 6-9-04
10. topotecan	Hycamtin®	11-20-02	N/A	Yes	Yes: 6-9-04
11. vinorelbine	Navelbine®	8-15-02	11-5-02	No ^d	Yes: 2-3-04

^a Source: <http://www.fda.gov/cder/pediatric/exgrant.htm> (NOTE: site provides only list of products, not exclusivity dates)

^b Source: <http://www.fda.gov/cder/pediatric/labelchange.htm>; N/A = not applicable

^c Source: <http://www.fda.gov/cder/pediatric/Summaryreview.htm>

^d Summaries of products granted BPCA pediatric exclusivity prior to July 2002 are not posted.

^e Source: <http://www.fda.gov/oc/opt/pediatricsafety.html>; AC = Advisory Committee

Clinical Review for NDA 19-880

Supplement SE8-019

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The Division of Oncology Drug Products (DODP), Center for Drug Evaluation and Research (CDER), FDA does not recommend addition of any information based on the pediatric studies conducted to the label.

The phase 1 study (CA124001), which enrolled patients to a combined regimen of carboplatin and irinotecan, also included the collection of pharmacokinetic data. However, because this was a combination study, it is difficult to reach definitive conclusions regarding pharmacokinetics and dosing for carboplatin based on the results of this study. Limitations included exclusion of a number of patients from the analysis due to lack of evaluable sampling and dosing errors. See also review by Dr. Bhattaram for further details.

The phase 2 study (CA124002), which allocated patients to carboplatin / irinotecan or irinotecan alone in a non-comparative fashion with each arm divided into two strata (CNS tumors versus non-CNS tumors), again provides data which are difficult to interpret. No pharmacokinetic data was collected in this study. Furthermore, the lack of a carboplatin alone arm and lack of a formal comparative design makes it difficult to draw any definitive conclusions regarding the activity of carboplatin. Responses were seen in only a few patients, whether on the irinotecan or combination arm. Response duration was also difficult to interpret. Another complicating factor in interpretation of both activity and safety was the prior exposure to carboplatin or cisplatin in a majority of patients.

From a safety perspective, the adverse events (AE's) observed were consistent with those previously observed and described in the respective carboplatin and irinotecan labels. Diarrhea, which was observed uniformly and with numerically comparable frequencies in all of the treatment arms of CA124002, is a well recognized AE associated with irinotecan use. Neurologic AE reports such as seizures and neuropathy were numerically more common in the CNS tumor groups as would be expected given the nature of the underlying disease. Hematologic toxicities of anemia, neutropenia and thrombocytopenia appeared to occur more commonly in the combination treatment groups compared to irinotecan alone. This finding is not surprising given the known myelosuppressive effect of either drug.

In summary, the response rates which can be attributed to carboplatin are not high enough to justify a treatment indication for carboplatin nor low enough to exclude the possibility that

CLINICAL REVIEW

Executive Summary Section

carboplatin has meaningful activity in these diseases, the safety data provide no new information for the label, and the pharmacokinetic (PK) data are not conclusive.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

No new phase 4 commitments are contemplated.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The applicant has submitted two clinical studies in pediatric patients with relapsed/refractory solid tumors with this supplemental NDA. The studies are described briefly as follows:

CA124001 was a dose finding study which enrolled 28 patients aged 1-21 with refractory solid tumors. The primary objective was to determine the maximum tolerated dose of carboplatin when administered in combination with irinotecan. Secondary objectives included evaluation of the safety profile and dose-limiting toxicity, determination of plasma pharmacokinetics of carboplatin and irinotecan, and evaluation of preliminary evidence of anti-tumor activity of the combination using objective response rate.

CA124002 was a study of carboplatin/irinotecan or irinotecan alone in pediatric patients with relapsed/refractory solid tumors. Patients were evaluated in CNS or non-CNS primary tumor strata. The primary endpoint was objective response rate. There was no formal comparative analysis of irinotecan alone versus the combination planned as part of the study design. Further evaluation of the safety of carboplatin was a secondary endpoint of the study. The chemotherapy administration schedules were as follows. Treatment was administered on a 21-day cycle in both arms.

Treatment A

Carboplatin: AUC 4 mg/ml.min as a 50-minute infusion on day 1, preceding the irinotecan
(b) (4) _____ :

Irinotecan: 12 mg/m²/day as a 60-minute IV infusion x 10 days

Treatment B

Irinotecan: 20 mg/m²/day as a 60-minute IV infusion x 10 days

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A total of 151 patients were enrolled. The distribution of patients in each of the two treatment arms and between the CNS and non-CNS strata are outlined in Table 1 below.

Table 1 : CA124002 Distribution of Patients

CNS Tumor Treatment A	CNS Tumor Treatment B	Non-CNS Tumor Treatment A	Non-CNS Tumor Treatment B
N = 28	N = 28	N = 47	N = 48

B. Efficacy

In the phase 1 study CA124001, objective response rate was a secondary endpoint. A total of 4 responses were observed. One patient with medulloblastoma had a complete response. Three patients were documented to have partial responses, one with medulloblastoma, one with lymphoepithelial carcinoma, and one with neuroblastoma. Observance of responses in medulloblastoma is consistent with previous clinical experience, where medulloblastoma is one childhood brain tumor known to be responsive to chemotherapy regimens. These observed responses were of limited duration, with relapse/progression documented about 2 months after observation of a response

Objective response rate was the primary endpoint of CA124002. Table 2 outlines the response rate in each of the two arms by stratum (CNS versus non-CNS primary). Table 3 outlines the individual diagnoses for responders.

Table 2 : Response Rates in CA124002

	CNS tumor Treatment A (N=28)	CNS tumor Treatment B (N=28)	Non-CNS tumor Treatment A (N=47)	Non-CNS tumor Treatment B (N=48)
CR + PR	4	3	3	6
Response Rate (%)	14	11	6	13
(95% Confidence Interval)	(4-33)	(2-28)	(1-18)	(5-25)

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Table 3 : Diagnosis in Individual Responders in CA124002

Treatment A CNS Tumor / Response	Treatment B CNS Tumor / Response	Treatment A non-CNS Tumor / Response	Treatment B non-CNS Tumor / response
Glioblastoma Multiforme/ PR Astrocytoma / PR Brainstem / PR Pineoblastoma / CR	Medulloblastoma / PR Medulloblastoma / PR Medulloblastoma / PR	Desmoplastic small round cell / PR Undifferentiated epithelial / PR Soft tissue sarcoma / PR	Neuroblastoma / CR Rhabdomyosarcoma/ PR Neuroblastoma / PR PNET / PR Hepatoblastoma / PR Rhabdomyosarcoma CR

There were a limited number of responses observed across treatment arms. Although the addition of carboplatin to irinotecan (treatment A) does not numerically increase the response rate when added to irinotecan alone (in fact, the irinotecan alone response rate in the non-CNS stratum is numerically higher than that with the combination), it is difficult to quantify the contribution of carboplatin to anti-tumor activity given the lack of a comparative statistical design and lack of a carboplatin single-agent comparator.

Responses ranged in duration from 1 month to 5 months. One patient with pineoblastoma who received therapy with carboplatin+irinotecan had a CR which was documented for over 5 months and one patient with rhabdomyosarcoma who was treated with irinotecan alone had a response which was documented for 4.7 months. Aside from the small number of patients in each cohort and lack of a formal comparative design for the combination versus irinotecan alone, nine of the 16 patients with a response were censored for response duration at last tumor assessment date, making it difficult to draw any conclusions regarding response duration in either arm as a whole or as a comparison between the two arms.

C. Safety

1. Adequacy of safety testing

CA124001 was a dose finding study with determination of a maximum tolerated dose (MTD) as its primary objective. As described above, this study enrolled 28 patients ranging in age from 1 – 21 years who were treated with a carboplatin / irinotecan

CLINICAL REVIEW

Executive Summary Section

combination. Due to the toxicity encountered at the –2a dose level (carboplatin AUC 5 mg/mL.min and irinotecan 12 mg/m²/day), the carboplatin AUC 4 mg/mL.min and irinotecan 12 mg/m²/day dose level was identified as the maximum tolerated dose. This dose level was expanded to 13 patients. Table 4 outlines the dose ranges evaluated, the number of patients enrolled at each level, and the nature of adverse events observed.

Table 4 : CA124001 DLT at Cycle 1 Dose

Initial Dose Level (carboplatin AUC/irinotecan mg/m²/day)	Number of Patients	Number Experiencing Cycle 1 DLTs	Cycle 1 DLTs And Grade (GR)
4 / 18	6	2	GR3 Diarrhea, ileus, dehydration, epistaxis
4 / 15	6	3	GR4 abdominal pain, prolonged neutropenia, thrombocytopenia GR3 hemorrhage, catheter infection Greater than 2-week delay in retreatment
4 / 12	13	1	GR3 bone pain GR4
5 / 12	3	3	GR3 diarrhea, abdominal pain > 2 platelet transfusions in 7 days > 2 week delay in retreatment

The safety database also consisted of 151 patients enrolled to CA124002. Of these, 75 were treated with the combination of irinotecan plus carboplatin, and 76 were treated with irinotecan alone. Duration of therapy ranged from one cycle to 10 cycles. Table 5 summarizes number of treatment cycles by treatment arm and tumor group.

Table 5 : Treatment Cycles per Patient on CA124002

	Treatment A ; CNS Tumors	Treatment B ; CNS Tumors	Treatment A ; non-CNS	Treatment B ; non-CNS
Median	4.5	4	2.5	3
Min – Max	1-9	1-10	1-9	1-9

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Within each stratum, the median number of therapy cycles was similar for both treatment arms. However, within each stratum, patients with CNS tumors had a slightly greater number of median cycles of therapy than non-CNS tumors.

Over 50% of patients had at least one dose delay due to carboplatin or irinotecan. Approximately 10% of patients across the 4 individual treatment groups required at least 1 dose reduction for irinotecan. As a whole, approximately 60% of treatment cycles given to patients on the combination arm were delayed, compared with 27% of cycles given to patients receiving irinotecan alone.

2. Serious side effects

Serious adverse events are discussed in the context of the CA124002 study results. As expected given the known adverse events (AEs) associated with carboplatin and irinotecan, hematologic toxicity including anemia, thrombocytopenia, or neutropenia was observed. Adverse events previously associated with irinotecan included diarrhea and other gastrointestinal toxicities. Adverse events previously associated with carboplatin included nausea, vomiting and neuropathy. All patients experienced adverse events, and the majority experienced at least one grade 3 or 4 AE during the study. The most commonly observed and clinically relevant grade 3 / 4 AE's are discussed below. As discussed above, the limited number of patients in each treatment group makes it difficult to draw any conclusions regarding comparisons between CNS and non-CNS patients or between treatment A and treatment B.

a. Gastrointestinal : Diarrhea, Vomiting

Grade 3 / 4 diarrhea appeared to occur with comparable frequency in both irinotecan alone and combination treatment groups, reflecting the prior known association of diarrhea with irinotecan administration. However, diarrhea did occur more frequently in CNS tumor patients than non-CNS tumor patients. The frequency of grade 3 / 4 diarrhea across the four treatment groups was as follows : CNS treatment A 32%, CNS treatment B 30%, non-CNS treatment A 9%, non-CNS treatment B 11%.

Although vomiting of any grade was reported in over 60% of patients on CA124002, grade 3 / 4 vomiting was reported in less than 5% of patients in most treatment groups, except the CNS treatment B group, where 5 patients (19%) were reported to have a grade 3/ 4 vomiting AE.

b. Neurologic: Motor Neuropathy, Seizures

Motor neuropathy was more commonly reported in CNS than in non-CNS treatment groups, possibly reflecting underlying disease. The frequency of grade 3 / 4 motor neuropathy across treatment groups was CNS treatment A 18%, CNS treatment B 22%, non-CNS treatment A 7%, non-CNS treatment B 4%. The incidence of seizures exhibited

CLINICAL REVIEW

Executive Summary Section

a similar pattern, with 18%-19% of CNS tumor patients experiencing a seizure compared with 6% or less of non-CNS tumor patients.

c. Infection / Febrile Neutropenia

Infection and febrile neutropenia appeared to occur slightly more commonly in the combination (treatment A) groups than with irinotecan alone, although the differences are not large enough for a definitive judgement. When evaluating febrile neutropenia alone, the differences between combination and irinotecan alone treatment groups are more pronounced: CNS treatment A 21%, CNS treatment B 7%, non-CNS treatment A 17%, non-CNS treatment B 2%.

d. Hematologic AE's : Neutropenia, Anemia, Thrombocytopenia

As expected, these appeared to occur more commonly in the carboplatin/irinotecan treatment groups than with irinotecan alone. The frequencies of grade 3 / 4 hematologic AE's across treatment groups are as follows in Table 6.

Table 6 : Grade 3 / 4 Hematologic AEs in CA124002

Hematologic AE	CNS Tumor Treatment A %	CNS Tumor Treatment B %	Non-CNS Tumor Treatment A %	Non-CNS Tumor Treatment B %
Hemoglobin	57	15	45	25
Neutrophils (ANC)	82	52	78	30
Platelets	68	7	56	4

These differences are noteworthy, especially for neutropenia, where G-CSF use was required in patients receiving combination therapy but only suggested for patients receiving irinotecan alone.

3. Drug-drug interactions

Cautions relevant to drug interactions already outlined in the carboplatin label include the following: 'The renal effects of nephrotoxic compounds may be potentiated by PARAPLATIN'

No changes are proposed or recommended.

4. Warnings

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Warnings pertaining to bone marrow suppression, vomiting, neurologic effects, renal toxicity, and anaphylactic reactions and their treatment are outlined in the carboplatin label. No additions are proposed or recommended.

D. Dosing

The dosing guidelines in the current labeling provide for a mg/m^2 dosing approach when determining dosing. The guidelines also describe determination of dosing using mathematical formulae such as the Calvert formula based on the patient's pre-existing renal function.

The clinical pharmacology and biopharmaceutics review executive summary described the limitations of the pharmacokinetic data from CA124001 and its analysis as follows. The pharmacokinetic analysis of the data was inconclusive. Due to lack of an adequate number of samples, data from 25-30% of the patients were discarded as they could not be utilized in the non-compartmental pharmacokinetic analysis methodology. The reviewer tried to provide a summary of the pharmacokinetic information from previous reviews in the division. No clear interpretation could be made based on the information available. Hence, the current study should be treated as inconclusive.

Due to these limitations and the limitations of the clinical data as described above, no additional dosing guidelines are recommended to be added to the label.

E. Special Populations

1. Pediatrics

See above. Both Ca124001 and 124002 were conducted in children ages 1 – 21 years of age.

2. Elderly

The current label describes the experience in elderly patients with ovarian cancer as follows :

“Of the 789 patients in initial treatment combination therapy studies (NCIC and SWOG), 395 patients were treated with carboplatin in combination with cyclophosphamide. Of these, 141 were over 65 years of age and 22 were 75 years or older. In these trials, age was not a prognostic factor for survival. In terms of safety, elderly patients treated with carboplatin were more likely to develop severe thrombocytopenia than younger patients. In a combined database of 1942 patients (414 were ≥ 65 years of age) that received single-agent carboplatin for different tumor types, a similar incidence of adverse events was seen in patients 65 years and older and in patients less than 65. Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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Because renal function is often decreased in the elderly, renal function should be considered in the selection of PARAPLATIN dosage”

No patients over the age of 21 were enrolled to either of the two clinical studies submitted to this sNDA. No additional wording regarding use in the elderly was proposed nor is any recommended.

2. Renal or Hepatic Impairment

Warnings regarding potential hepatic or renal toxicity are outlined in the current labeling. As discussed above, the current labeling includes dosing guidelines based on mathematical formulae which take into account pre-existing renal function. No changes were proposed by the sponsor nor are any recommended.

4. Gender / Ethnicity / Specific Age Distribution

The demographics of the 28 patients enrolled to CA124001 can be summarized as follows. There were 17 males and 11 females enrolled. Patients’ age range was from 1 to 21 years. Ten patients were age 4 years or younger, 6 were between 5 and 10 years of age, and 12 patients were age 11 years or older. Eighteen patients were listed as white (including hispanic) 6 as black, and 4 as other.

The demographics of patients enrolled to CA124002 are summarized in table 7 below.

Table 7 : Gender, Race and Age on CA124002

Demographic	CNS Tumor Treatment A N = 28	CNS Tumor Treatment B N = 28	Non-CNS Tumor Treatment A N = 47	Non-CNS Tumor Treatment B N = 48
Gender				
Male	13	18	32	24
Female	15	10	15	24
Race				
White	21	23	28	29
Black	1	2	5	5
Asian	1	1	2	4
Other	5	2	12	0
Age (years)				
Median	8.5	12	14	10
Range	1-17	2-19	1-20	1-21

5. Pregnancy

CLINICAL REVIEW

Executive Summary Section

Carboplatin injection should not be used in pregnant women. The drug is currently labeled as pregnancy class D, due to its teratogenic effects.

CLINICAL REVIEW

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Executive Summary

Executive Summary

The sponsor submitted data from two studies which evaluated the combination of carboplatin every 3 weeks with irinotecan daily x 5 x 2 every 3 weeks. The first study is a Phase I dose finding study with pharmacokinetic evaluation conducted in 28 patients with refractory or relapsed solid tumors to establish the maximum tolerated dose (MTD). In the Phase II study, patients were randomized to receive either irinotecan 12 mg/m²/day x 10 days in combination with carboplatin exposure (AUC) 4 mg/mL*min (Treatment A) or irinotecan 20 mg/m²/day x 10 days every 21 days.

The pharmacokinetic information obtained from the Phase I study was found to be inconclusive because of the following reasons:

1. Only 33% of the measured carboplatin AUCs were within 30% of the target AUC of 4 mg/mL•h. However, a previous study showed that use of same formula (the modified Calvert formula) resulted in 68% of the measured carboplatin AUCs within 30% of the target AUC in the subset of patients with measured samples (Marina et al, Journal of Clinical Oncology, Vol 11, No 3 (March 1993)). It appears that this could be due to dosing errors as reported by the sponsor or unknown clinical reasons.
2. The AUC of irinotecan (18 mg/m²) was 550 ng/mL•h in comparison to 294 ng/mL•h as observed in previous studies. No significant differences were observed for the metabolites of irinotecan (SN 38 and APC). The differences observed for irinotecan could be due to (a) sample size (N=5) (b) variability between studies.

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the submitted information and has found the analysis performed by the sponsor inconclusive. Hence, no information should be added to the label.

The following information should be forwarded to the sponsor:

1. Whenever comparisons from across studies are made, a table clearly showing the comparison of pharmacokinetic parameters should be provided.
2. Discarding of data from analysis is discouraged. Prior information available in the literature should be utilized in order to maximize the information derived in the study. Use of other analysis methodology such as population pharmacokinetic analysis, may have enabled a much better interpretation of the study.

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Brian Booth
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Clinical Review for NDA 21-673

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The Medical Reviewer, Division of Oncology Drug Products (DODP), Center for Drug Evaluation and Research (CDER), FDA, in concurrence with the Oncologic Drugs Advisory Committee (ODAC), believes that the pediatric ALL application is approvable under CFR 314.500 Subpart H--Accelerated approval while the pediatric AML indication is not approvable. As indicated in CFR 314.510, post marketing clinical studies should usually be underway at the time of accelerated approval under Subpart H. No such post marketing clinical studies are underway. In addition, a clofarabine regimen suitable for testing in such clinical studies has not been identified. There is uncertainty whether such a regimen can be identified. Further none of the proposed post marketing studies has a realistic chance of demonstrating clofarabine clinical benefit in children with ALL. Clofarabine clinical benefit is difficult to assess in the present trial because patients often went to transplant, so that clofarabine response duration can not be assessed. In addition some patients went to transplant before clofarabine response could be confirmed and some patients went to transplant without a clofarabine response. Thus in transplanted patients the response durations in responding patients and the time-to relapse and survival are an effect of clofarabine + transplant and the effect of clofarabine can not be isolated.

Clofarabine toxicity, while considerable, is what one might expect in a heavily pretreated population of pediatric acute leukemia.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

Approval will be conditional on FDA review of the Phase 1 part of your proposed Phase 1-2 study, showing that an acceptable clofarabine, cytarabine, PEG Asparaginase regimen has been developed for study in the Phase 2 part of the study and potentially in a Phase 3 study that has a realistic chance of demonstrating clinical benefit in children with ALL. Your proposed Phase 1-2 study and time-lines follow.

Clo-216: A Phase 1-2 dose-escalation study of clofarabine plus cytarabine and L-Asparaginase in pediatric patients with refractory or relapsed acute lymphoblastic leukemia.

Trial initiation	6-1-05
Trial completion	10-1-06
Submit study report	4-13-07

Approval will also be conditional on the your submission of a clinical study protocol with a realistic chance of demonstrating clofarabine clinical benefit in children with ALL and your commitment to conduct the study and submit the results in an acceptable time frame.

Phase 3 trials, conducted in less refractory pediatric ALL and AML populations, Comparing a clofarabine containing regimen \pm transplant to an appropriate control regimen \pm transplant should be submitted in timely fashion as a Special Protocol Assessment.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Two Phase II pivotal studies have been conducted by ILEX in pediatric patients with refractory or relapsed ALL (CLO-212) or refractory or relapsed AML (CLO-222), in which clofarabine was used as a single agent.

In addition phase I/II pediatric and adult clofarabine studies conducted at (b) (4) (b) (4)) were submitted.

B. Efficacy

In pediatric AML there was 1 CRp (2.9%) and 8 PR's among 35 treated patients. Twelve of 35 AML patients went on to transplant including the CRp patient, 6 PR's, 3 not-evaluative patients and 2 treatment failures. The usual definition of efficacy is long duration complete responses or prolonged overall survival. In trial CLO-222 there were no CR's, only one CRp (2.9%) and 8 PR's. The CRp patient and 6 of the PR's went on to have a transplant. Long duration responses and prolonged survival were confined to patients who received a transplant. Four clofarabine plus transplant patients had longer time to progression (TTP) with that treatment than they had with the therapy that immediately preceded clofarabine. Three of these 4 patients also had longer TTP with clofarabine plus transplant than they had with their preceding transplant.

In Pediatric ALL there were 6 CR's (12.2%), 4 CRp's (8.2%) and 5 PR's among 49 treated patients. Eight ALL patients went on to transplant including 2 CR's, 2 CRp's, 2 PR's, 1 not-evaluative patient and 1 treatment failure. The usual definition of efficacy is long duration complete responses or prolonged overall survival. In study CLO-212 among the 6 CR patients 3 had ongoing responses at the time of data cutoff and 3 had relapsed. Using the criteria of longer TTP with clofarabine \pm transplant than to immediate prior therapy 2 of 6 CR patients, 3 of 4 CRp patients and 0 of 5 PR patients demonstrated benefit. With further follow-up benefit may be demonstrated in 3 additional CR patients and 1 PR patient.

C. Safety

The toxicity profile of clofarabine was as expected for a heavily pretreated acute leukemia pediatric patient population. The principal toxicities were nausea and vomiting, hematologic toxicity, fever and febrile neutropenia, hepatobiliary toxicity, infections and renal toxicity. Clofarabine can produce systemic inflammatory response syndrome/capillary leak syndrome (SIRS), manifested by the rapid development of tachypnea, tachycardia, hypotension, shock, and multi-organ failure. Cardiac toxicity most often

manifest as left ventricular systolic dysfunction with accompanying tachycardia may also occur. With attentive patient care, however, the drug was tolerable.

D. Dosing

The recommended clofarabine pediatric dose and schedule is 52 mg/m² administered by intravenous infusion (IVI) over 1 to 2 hours daily for 5 consecutive days. Treatment cycles are repeated every 2 to 6 weeks following recovery or return to baseline organ function. The dosage is based on the patient's body surface area (BSA), calculated using the actual height and weight before the start of each cycle.

E. Special Populations

Pediatrics -

The studies were performed in pediatric patients

Elderly -

No clofarabine data is available for elderly patients.

Renal or Hepatic Impairment -

The major route of clofarabine elimination is renal clearance. Clofarabine is likely not metabolized by the CYP450 enzyme system,

Gender -

Results appeared comparable for males and females

Ethnicity -

There was no significant effect of race/ethnicity on either efficacy or safety results.

Pregnancy – Category D

Pregnancy studies have not been done in humans. Female patients with childbearing potential must have a negative serum pregnancy test before starting each cycle of clofarabine therapy. Men and women with reproductive potential must use an effective contraceptive method while taking the drug. If a patient becomes pregnant while taking clofarabine, she should be apprised of the potential hazard to the fetus. Because impairment of fertility is unknown, reproductive planning should be discussed with the patient, as appropriate.

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/s/

Martin Cohen

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

**NDA 21-673
UPDATED**

Drug name: CLOLAR®

Generic name: Clofarabine

Formulation: 1mg/mL solution for intravenous administration

Pediatric Indication: Refractory or relapsed acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML) in children.

Current Submission: NDA-NME

Applicant: Ilex Products Inc.
4545 Horizon Hill Blvd.
San Antonio, Texas 78229-2263

OCPB Division: Division of Pharmaceutical Evaluation I (HFD-860)

OND Division: Division of Oncology Drug Products (HFD-150)

Submission Dates: 29-Mar-2004, 2-Aug-2004, 5-Aug-2004, Oct-3-2003

Primary Reviewer: Roshni Ramchandani, Ph.D.

**Pharmacometrics
Team Leader:** Joga Gobburu, Ph.D.

Team Leader: Brian Booth, Ph.D.

I. Executive Summary

Clofarabine is a purine nucleoside analog. The applicant has conducted studies evaluating the use of clofarabine in the treatment of acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML) in pediatric patients. The applicant has conducted 3 clinical studies that form the basis for the NDA application and include a Phase 1 study and 2 phase 2 studies. Study # ID99-383 was a phase 1 open-label, non-randomized, dose escalation study for pediatric patients with hematological malignancies (ALL and AML) who have failed standard therapy or for whom no such therapy existed (n=25). Patients received doses of clofarabine as 1-3 hr IV infusion daily \times 5 days, every 2 to 6 weeks for a maximum of 12 cycles. The doses evaluated were 11.25, 15, 30, 40, 52 and 70 mg/m²/day. The objective of this study was to establish the maximum tolerated dose and obtain pharmacokinetic data in this population. Study # CLO-212 was a phase 2 open-label, non-randomized study in pediatric patients (1-20 yrs) with refractory or relapsed acute lymphoblastic leukemia (ALL) (n=49). Patients received 52 mg/m²/day of clofarabine as a 2-hr IV infusion daily \times 5 days, every 2 to 6 weeks for a maximum of 12 cycles. The objective of this study was to examine the effectiveness of clofarabine in this population as well as to obtain data on the pharmacokinetics (PK) of clofarabine in the pediatric population. Study # CLO-222 was a phase 2 open-label, non-randomized study in pediatric patients (1-20 yrs) with refractory or relapsed acute myelogenous leukemia (AML) (n=35). Patients received 52 mg/m²/day of clofarabine as a 2-hr IV infusion daily \times 5 days, every 2 to 6 weeks for a maximum of 12 cycles. The objective of this study was to examine the effectiveness of clofarabine in this population as well as to obtain data on the PK of clofarabine in the pediatric population.

The population pharmacokinetics of clofarabine were studied in 40 pediatric patients, aged 2 to 19 years (21 males/19 females), from the above studies. Clofarabine pharmacokinetics were best described by a 2-compartment model with first order elimination. Body weight was a significant predictor for all model parameters (CL, Q, V1 and V2). BSA-normalized doses of 52 mg/m² produced equivalent exposure across a wide range of BSAs. Based on a non-compartmental analysis, systemic clearance and volume of distribution at steady-state were estimated to be 28.8 L/h/m² and 172 L/m², respectively. The terminal half-life was estimated to be 5.2 hours. The baseline White Blood Cell (WBC) count was found to be a significant predictor of the central compartment volume V1 by the applicant. However, the Agency's analysis determined that WBC counts were not correlated with the central volume estimates and inclusion of WBC in the parameter model did not reduce the population variance for the central volume. Renal excretion of unchanged clofarabine (over a 24-hour interval) accounted for 49-60% of the total clearance. In vitro studies using isolated hepatocytes indicate very limited hepatic metabolism, thus the pathways of non-renal elimination are unknown. No major pharmacokinetic differences were found between ALL and AML patients or between male and female patients. Intra-cellular concentrations of the active metabolite clofarabine triphosphate were also measured in some patients in the phase 1 study, however the data were too sparse for any meaningful evaluation. The inhibition and induction potential of clofarabine for cytochrome p450 enzymes has not been studied. The pharmacokinetics of clofarabine have not been evaluated in patients with renal or

hepatic dysfunction, and use of the drug in these patients should be undertaken with caution.

No significant relationships were found between measures of clofarabine exposure and measures of clofarabine response or toxicity in this population. This may be because the majority of the patients received the 52 mg/m² dose and this did not provide an adequate range of exposures to effectively evaluate the exposure-response relationship for clofarabine.

A. Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed the Clinical Pharmacology section of NDA 21-673 and finds it to be acceptable, with some revisions to the applicant's proposed label.

FDA Proposed labeling

1. The following should be inserted under the Human Pharmacokinetics section, under CLINICAL PHARMACOLOGY

The population pharmacokinetics of CLOLAR™ were studied in 40 pediatric patients aged 2 to 19 years (21 males/19 females) with relapsed or refractory ALL or AML. At the given 52 mg/m² dose, similar concentrations were obtained over a wide range of BSAs. Clofarabine was 47% bound to plasma proteins, predominantly to albumin. Based on non-compartmental analysis, systemic clearance and volume of distribution at steady-state were estimated to be 28.8 L/h/m² and 172 L/m², respectively. The terminal half-life was estimated to be 5.2 hours. No apparent difference in pharmacokinetics was observed between patients with ALL and AML or between males and females.

No relationship between clofarabine or clofarabine triphosphate exposure and toxicity or response was found in this population.

Based on 24-hour urine collections in the pediatric studies, 49-60% of the dose is excreted in the urine unchanged. *In vitro* studies using isolated human hepatocytes indicate very limited metabolism (0.2%), therefore the pathways of non-renal elimination remain unknown.

Although no clinical drug-drug interaction studies have been conducted to date, on the basis of the *in vitro* studies, cytochrome p450 inhibitors and inducers are unlikely to affect the metabolism of clofarabine. The effect of clofarabine on the metabolism of cytochrome p450 substrates has not been studied. The pharmacokinetics of clofarabine have not been evaluated in patients with renal or hepatic dysfunction.

2. The following should be inserted under the Drug Interactions section under PRECAUTIONS

Although no clinical drug-drug interaction studies have been conducted to date, on the basis of the *in vitro* studies, cytochrome p450 inhibitors and inducers are unlikely to affect the metabolism of clofarabine. The effect of clofarabine on the metabolism of cytochrome p450 substrates has not been studied.

3. The following should be inserted under the Hepatic and Renal Impairment under WARNING and under the DOSAGE AND ADMINISTRATION section

CLOLAR™ has not been studied in patients with hepatic or renal dysfunction. Its use in such patients should be undertaken only with the greatest caution.

(b) (4) _____

B. Phase IV Commitments

None.

C. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Clofarabine pharmacokinetics were determined in 40 pediatric patients, ages 2 to 19 years, from 3 studies: a phase 1 dose escalation study and two phase 2 studies in ALL and AML patients. A population pharmacokinetic model was fit to the data from these studies. Clofarabine pharmacokinetics was best described by a 2-compartment model with first order elimination. Body weight was the best predictor in parameter models for all model parameters (CL, Q, V1 and V2). The applicant's model included baseline WBC count as a predictor of the central compartment volume V1. The Agency's analysis determined that WBC counts were not correlated with the central volume estimates and inclusion of WBC in the parameter model did not reduce the population variance for the central volume. Based on a non-compartmental analysis, systemic clearance and volume of distribution at steady-state were estimated to be 28.8 L/h/m² and 172 L/m², respectively. The terminal half-life was estimated to be 5.2 hours. No major pharmacokinetic differences were found between ALL and AML patients or between male and female patients. Intra-cellular concentrations of the active metabolite clofarabine triphosphate were also measured in some patients in the phase 1 study, however the data were too sparse for any meaningful evaluation.

Renal excretion of unchanged clofarabine, measured over a 24-hour period, accounts for 49-60% of the total clearance. *In vitro* studies using isolated hepatocytes indicate very limited hepatic metabolism, thus the pathways of non-renal elimination are unknown. The inhibition and induction potential of clofarabine for cytochrome p450 enzymes has not been studied. The pharmacokinetics of clofarabine has not been evaluated in patients with renal or hepatic dysfunction.

No significant relationships were found between measures of clofarabine exposure and measures of clofarabine response or toxicity. The applicant's analysis only included those patients who had PK measurements. The Agency's re-analysis of this data included estimation of the exposure (AUC) of clofarabine in all the patients in the studies, based on the parameter model for clearance which was a function of body weight. However this did not change the outcome, and there were still no significant associations between AUC and measures of toxicity or response. This may be partly because the majority of the patients received the 52 mg/m² dose, which did not provide an adequate range of exposures to effectively evaluate the exposure-response relationship for clofarabine.

Roshni Ramchandani, Ph.D.
Clinical Pharmacology Reviewer
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation I

Concurrence:

Brian Booth, Ph.D.
Acting Clinical Pharmacology Team Leader
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation I

Concurrence:

Joga Gobburu, Ph.D.
Pharmacometrics Team Leader
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation I

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Brian Booth
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Clinical Review

sNDA 20-038

Drug Name	Fludarabine Phosphate
Medical Reviewer	Martin H. Cohen, M.D.
Medical Team Leader	John Johnson, M.D.
Documents reviewed	13 volume sponsor submission

Clinical Review for NDA 20-038s

1. Executive Summary

The intent of this sNDA is to provide information from clinical trials of fludarabine phosphate (Fludara®) in pediatric cancer patients to fulfill the requirements outlined in the FDA Written Request for obtaining pediatric exclusivity.

Fludarabine phosphate was approved in 1991 for the treatment of patients with B-cell chronic lymphocytic leukemia [CLL] who have not responded to or whose disease has progressed during treatment with at least one standard alkylating agent-containing regimen. Its patent expires on February 23, 2003.

As CLL does not occur in children, the proposed pediatric labeling for Fludara® contains information regarding pediatric dosing in relapsed pediatric acute lymphocytic leukemia (ALL) and acute myelocytic leukemia (AML).

The sponsor has submitted clinical data on pediatric dosing and pharmacokinetic studies derived from two studies [CCG-097 and CCG-0895] conducted by the Children's Cancer Group (CCG), presently known as Children's Oncology Group (COG). Data from these two studies have been reported in the following publications:

CCG-097 - Avramis V., Champagne J., Sato J., Krailo M., Ettinger L., Poplack D., Finklestein J., Reaman G., Hammond D., Holcenberg J. Pharmacology of Fludarabine Phosphate After a Phase I/II Trial by a Loading Bolus and Continuous Infusion in Pediatric Patients. *Cancer Res.* 50: 7226-7231 1990.

CCG-0895 - Avramis V., Wiersma S., Krailo M., Ramilo-Torno L., Sharpe A., Liu-Mares W., Kwock R., Reaman G., Sato J. for the Children's Cancer Group. Pharmacokinetic and Pharmacodynamic Studies of Fludarabine and Cytosine Arabinoside Administered as Loading Boluses followed by Continuous Infusions after a Phase I/II Study in Pediatric Patients With Relapsed Leukemias. *Clin Cancer Res* 4: 45-52 1998.

The first study, CCG-097, was a Phase I dose finding and PK study of a loading bolus followed by continuous infusion of fludarabine in patients with previously treated advanced acute leukemias or solid tumors. Enrollment included 9 patients with acute nonlymphoblastic leukemia (ANLL), 36 patients with ALL and 17 solid tumor patients. The MTD, defined in the above referenced publication in patients with solid tumors, was a loading bolus of 7 mg/m² followed by a continuous infusion of 20.0 mg/m² for 5 days. In patients with acute leukemias, the MTD was not reached. The highest dose administered was a loading bolus of 10.5 mg/m² followed by a continuous infusion of 30.5 mg/m² for 5 days (Dose Level 6).

The difference in the MTDs between the leukemia and solid tumor patients appeared to be related to the way dose-limiting toxicities (DLT) were evaluated. In leukemia

patients, hematologic toxicities were not considered in the evaluation of DLTs since marrow ablation was a goal of therapy. CCG decided to cease escalation beyond the planned highest dose level because of concern for potential irreversible CNS toxicity previously reported in adults. In the solid tumor patients, the DLT was myelosuppression.

An independent retrospective analysis of the MTD could not be conducted, primarily due to missing or incomplete case report forms (CRFs).

An independent retrospective analysis of response in this trial could not be conducted, primarily due to missing or incomplete case report forms (CRFs).

The second study, CCG-0895, was a Phase 1/2 dose-finding, PK, and pharmacodynamic (PD) study of a loading bolus followed by continuous infusion of fludarabine followed by a loading bolus and then continuous infusion of ara-C in children with previously treated advanced acute leukemias. As such it provided no information on the efficacy or safety of fludarabine phosphate alone in pediatric acute leukemia.

1.1 Recommendations

1.1.1 Recommendation on Approvability

The low response rate, especially the low complete response rate, and relatively brief duration of response in pediatric refractory ALL and the absence of response in ANLL and solid tumors do not suggest a role for fludarabine phosphate in the treatment of these malignancies. The combined fludarabine/ara-C trial achieved a modest response rate at the cost of considerable toxicity (see section 8.3).

While the fludarabine/ara-C study cannot provide data on the efficacy of fludarabine alone it does provide efficacy and safety data for the combination. As such it is valuable since it is unlikely that physicians would treat relapsed pediatric ALL with a single agent.

Conclusions:

1. There is no reason to modify the label to include the pediatric data that was presented in this sNDA.
2. By conducting the two studies the sponsor met the requirement for pediatric exclusivity.

1.1.2 Recommendation on Phase 4 Studies and/or Risk Management Steps

Not relevant

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Martin Cohen

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Clinical Pharmacology and Biopharmaceutics Review

I. Project Identification

NDA number/serial number	20,038/SE8-028-PM
Submission date	February 7, 2003
Drug name	Fludara
Generic name	Fludarabine
Dosage form	lyophilized powder for IV injection
Sponsor	Berlex Laboratories 15049 San Pablo Avenue Richmond, CA 94804-0099
Reviewer	Anne Zajicek, M.D., Pharm.D.
Submission Type	NDA-Supplement

II. Executive Summary

The applicant submitted the results of two clinical studies of fludarabine in children with relapsed malignancies. Study CCG-097 was a Phase 1 pharmacokinetic study of 23 children with relapsed acute leukemias (n=18) and solid tumors (n=5) who were randomized to receive one of six increasing bolus + 5 day infusion regimens. The pharmacokinetics of fludarabine in these children was markedly different from that reported in adult studies. Mean clearance in the children was 0.61 L/hr/m², compared with 8.7 and 4.1 L/hr/m² in two adult studies. Half-life and volume of distribution were similar to adult values (12.4 vs 10.4 hours, and 10.8 vs 7.5 L/m² respectively). The explanation of this difference is unclear. Study CCG-0895 was a Phase 1/2 study combining bolus + 2 day infusion fludarabine, followed by a 3 day infusion of increasing dose cytarabine in children with relapsed acute leukemias. There were three children with evaluable data; their clearance values were similar to those seen in CCG-097, ranging from 0.44-2.15 L/h/m².

No labeling changes for pediatric indications or dosing will be made at this time due to inadequate efficacy data generated in the study report.

Anne Zajicek, M.D., Pharm.D.
Medical Officer, Clinical Pharmacology Reviewer
DPE1

N.A.M. Atiqur Rahman, Ph.D.
Team Leader
DPE1

CC: NDA 20,038/SE8-028
HFD-150 Division File
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HFD-150 MCohen, JJohnson
HFD-860 MMehta, CSahajwalla, ARahman, AZajicek
CDR Biopharmaceutics

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Anne Zajicek
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Gemcitabine Pediatric Exclusivity

Executive Summary

The effectiveness of Gemzar® (gemcitabine HCl) in pediatric patients has not been demonstrated.

Gemcitabine was initially evaluated in a Phase 1 dose finding study. The primary study endpoint was maximum tolerated dose (MTD). The secondary endpoint was pharmacokinetics, with measurement of gemcitabine blood concentrations, clearance, and distribution in body compartments. In this study fourteen heavily pretreated, refractory patients were enrolled, all with pediatric acute leukemia. The age range of study patients included infants 1 year of age to 20 years of age. Demographic and disease characteristics of study patients are summarized in Table 1. One of 6 patients receiving gemcitabine 10 mg/m²/minute continuous infusion for 360 minutes weekly for 3 weeks had dose-limiting hematologic toxicity. Eight patients then received gemcitabine 10 mg/m²/minute for 480 minutes. Three had dose-limiting toxicity. Thus the MTD is 10 mg/m²/minute continuous infusion for 360 minutes weekly for 3 weeks with a one week rest. Eleven patients had pharmacokinetic studies done.

The phase 2 pediatric study performed by the Childrens Oncology Group, enrolled 20 evaluable patients with acute lymphoblastic leukemia (ALL) and 10 evaluable patients with acute myelogenous leukemia (AML). There were no patients with non-Hodgkin's lymphoma. The age range of study patients included infants 1 year of age to adolescents age ≤ 20. Demographic and disease characteristics of study patients are summarized in Table 2. Patients received gemcitabine 10 mg/m²/minute continuous infusion for 360 minutes weekly for 3 weeks with a one week rest. The primary study endpoint was complete response (CR) rate. There was 1 CR (ALL). As in the phase 1 study, hematologic toxicity was dose-limiting. Other observed gemcitabine toxicities included febrile neutropenia, elevation of serum transaminases, nausea, vomiting and rash/desquamation. This toxicity spectrum was similar to that reported in adults.

The conclusion of the phase 2 study was that gemcitabine at the dose and schedule studied was not effective for children with relapsed ALL or AML. Appropriate sections of the label incorporate the findings of the above studies.

Pediatric exclusivity was granted in January 27, 2005.

Table 1. Characteristics of Eligible Children with Relapsed Acute Leukemia Enrolled on CCG 0955 Study

Characteristics	Value (N = 14)
Age at Study Entry (years) Median (Range)	9 (1 - 16)
Gender	
Male	6 (43%)
Female	8 (57%)
Race	
White	5 (36%)
Hispanic	8 (57%)
Asian	1 (7%)
Histology	
ALL	7 (50%)
AML	7 (50%)
Gemcitabine dose	
3600	6 (43%)
4800	8 (57%)
Prior chemotherapy	
Yes	14 (100%)
Prior transplant	
Yes	3 (21%)
No	11(79%)
Prior radiation	
Yes	6 (43%)
No	8 (57%)

Table 2. Characteristics of Eligible Children with Relapsed Acute Lymphoblastic Leukemia or Acute Myelogenous Leukemia Enrolled on ADVLO22 Study

Characteristics	Value (N = 32)
Age at Study Entry (years) Median (Range)	10 (1 - 20)
Gender	
Male	23 (72%)
Female	9 (28%)
Race	
White	18 (56%)
Hispanic	10 (32%)
Black	2 (6%)
Asian	2 (6%)
Number of Chemotherapy Regimens Received Prior to Enrollment	
1	5 (16%)
2	12 (38%)
3	9 (28%)
4	4 (12%)
6	2 (6%)
Was Radiation Therapy Received Prior to Enrollment	
Yes	12(37%)
No	20 (63%)
Did the Patient Have a Bone Marrow Transplant Prior to Enrollment	
Yes	8 (25%)
No	24 (75%)

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Martin Cohen
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John Johnson
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NDA 21-588-S016-2006-03-27
Executive Summary
Pediatric Ph+ CML

Reviewer Name	Martin H. Cohen, M.D. Shenghui Tang, Ph.D.
Review Completion Date	6/1/06
Established Name	Imatinib mesylate (STI571)
Trade Name	Gleevec
Therapeutic Class	Molecularly targeted drug
Sponsor	Novartis
Priority Designation	S

Formulation

Gleevec[®] (imatinib mesylate) film-coated tablets contain imatinib mesylate equivalent to 100 mg or 400 mg of imatinib free base. of age.

Dosing Regimen

The recommended dose of Gleevec as single-agent for newly diagnosed pediatric patients with Ph+ CML is 340 mg/m²/day. If the child could not swallow the capsule, the capsule contents were dissolved in water or apple juice. There is no experience in dosing children <2 years

The recommended Gleevec dosage is 260 mg/m²/day for children with Ph+ chronic phase CML recurrent after stem cell transplant or who are resistant to interferon-alpha therapy.

The prescribed dose should be administered orally, once-daily, with a meal and a large glass of water.

Gleevec Pediatric Indication(s)

Proposed: Gleevec is indicated as a single agent for the treatment of pediatric patients with newly diagnosed Ph+ CML in chronic phase.

Gleevec is also indicated for the treatment of pediatric patients with Ph+ chronic phase CML whose disease has recurred after stem cell transplant or who are resistant to interferon-alpha therapy. There are no controlled trials in pediatric patients demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

Executive Summary

The purpose of the present submission is to present data to support the proposed indication: “Gleevec is indicated as a single agent for the treatment of pediatric patients with newly diagnosed Ph+ CML”.

This current sNDA is also intended to meet the terms of the Pediatric Written Request dated 20-Sep-2000 in supporting the above indication and in qualifying for pediatric exclusivity. The application is based on data collected up to 10-Jun-2005 in Study 2108. It also references pediatric data from Study 0103 and Study 03 001 from a previous submission (NDA 21-335/S-003), as well as data from published literature.

Recommendation On Regulatory Action

The clinical reviewer recommends that Gleevec receive accelerated approval for the treatment of pediatric patients with newly diagnosed Ph+ CML. This is based upon the induction of both hematologic and cytogenetic responses in this patient population. A total of 51 pediatric patients with newly diagnosed and untreated chronic phase CML were enrolled in an open-label, multicenter, single arm phase II trial (Study 2108). Patients were treated with Gleevec 340 mg/m²/day. Complete hematologic Response (CHR) was observed in 78% of pediatric patients after 8 weeks of therapy. The complete cytogenetic response (CCyR) rate was 65%, comparable to the results observed in adults. Additionally, partial cytogenetic response (PCyR) was observed in 16%. The majority of patients who achieved a CCyR developed the CCyR between months 3 and 10 with a median time to response of 6.74 months. Estimated survival at 12 months was 98% and estimated survival at 24 months was 84%

In addition, a single-arm Phase I study (0103) enrolled 14 pediatric patients with Ph+ chronic phase CML recurrent after stem cell transplant or resistant to interferon-alpha therapy. Patients were treated at doses of 260 mg/m²/day (n=3), 340 mg/m²/day (n=4), 440 mg/m²/day (n=5) and 570 mg/m²/day (n=2). In the 13 patients for whom cytogenetic data are available, 7 achieved a CCyR, and 4 achieved a PCyR.

In a second Phase I study (03001), 2 of 3 patients with Ph+ chronic phase CML resistant to interferon-alpha therapy achieved a complete cytogenetic response at doses of 242 and 257 mg/m²/day.

Imatinib generally was well tolerated. Grade 3 or 4 toxicities in the 54 pediatric patients of Study 2108 were primarily hematologic. Non-hematological grade 3 or 4 toxicities included allergic reaction/hyper-sensitivity, avascular osteonecrosis and desquamating rash. The incidence of edema/weight gain (14%) remained low, in contrast to the higher incidence rate seen in adult chronic phase patients (59% in study 0106). There were no deaths during the study period and only one patient discontinued study drug due to suspected study drug-related AEs (elevated AST/ALT). Muscle cramps were reported sporadically during the study and there were no episodes of GI hemorrhage. No new safety concerns were raised.

Recommendation On Post-marketing Actions

Continue post-marketing surveillance.

Risk Management Activity

Continue post-marketing surveillance of AE's

Required Phase 4 Commitments

A phase 4 commitment to continue follow-up of pediatric Ph+ CML patients treated in study 2108 to obtain long-duration (5+ years) survival data.

Other Phase 4 Requests

None

Summary Of Clinical Findings

Overview of Clinical Program

This current sNDA is intended to meet the terms of the Written Request dated 20-Sep-2000 to support the indication for treatment of Philadelphia positive (Ph+) CML in pediatric patients and to qualify for pediatric exclusivity. The application is based on data collected up to 10-Jun-2005 in Study 2108. It also includes pediatric data from two phase 1 studies, 0103 and 03 001, from a previous submission (NDA 21-335/S-003), as well as data from published literature.

Efficacy

A total of 51 pediatric patients with newly diagnosed and untreated CML in chronic phase have been enrolled in an open-label, multicenter, single arm phase II trial (Study 2108). Patients were treated with Gleevec 340 mg/m²/day, with no interruptions in the absence of dose limiting toxicity. CHR was observed in 78% of pediatric patients after 8 weeks of therapy. The complete cytogenetic response (CCyR) rate was 65%, comparable to the results observed in adults. Additionally, partial cytogenetic response (PCyR) was observed in 16%. The majority of patients who achieved a CCyR developed the CCyR between months 3 and 10 with a median time to response based on the Kaplan-Meier estimate of 6.74 months.

One open-label, single-arm study (0103) enrolled 14 pediatric patients with Ph+ chronic phase CML recurrent after stem cell transplant or resistant to interferon-alpha therapy. Patients ranged in age from 3-20 years old; 3 were 3-11 years old, 9 were 12-18 years old, and 2 were >18 years old. Patients were treated at doses of 260 mg/m²/day (n=3), 340 mg/m²/day (n=4), 440 mg/m²/day (n=5) and 570 mg/m²/day (n=2). In the 13 patients

for whom cytogenetic data are available, 7 achieved a CCyR, 4 achieved a PCyR and 2 had a minimal cytogenetic response

In a second Phase I study (03001), 2 of 3 patients with Ph+ chronic phase CML resistant to interferon-alpha therapy achieved a complete cytogenetic response at doses of 242 and 257 mg/m²/day.

Safety

Imatinib generally was well tolerated. Grade 3 or 4 toxicities in the 54 pediatric patients of Study 2108 were primarily hematologic. Non-hematological grade 3 or 4 toxicities included allergic reaction/hyper-sensitivity, avascular osteonecrosis and desquamating rash. Of note, the incidence of edema/weight gain (14%) remained low, in contrast to the higher incidence rate seen in adult chronic phase patients (59% in study 0106). There were no deaths during the study period and one patient (731829) discontinued study drug due to suspected study drug-related AEs (elevated AST/ALT). Muscle cramps were reported sporadically during the study and there were no episodes of GI hemorrhage. The incidence of grade 3 or 4 myelosuppression in chronic phase CML patients was higher than has been seen in comparable adult patients. Grade 3 or 4 increases in liver function tests (LFTs) were reported in one patient who was diagnosed with autoimmune hepatitis. No other unusual laboratory findings were reported. Overall, there is concordance with study 2108 and the phase I experience (study 0103) in pediatric patients following treatment with imatinib.

Dosing Regimen and Administration

PK data, available from two early studies, 03 001 and 0103, show that imatinib was rapidly absorbed after oral administration in pediatric patients, with a C_{max} of 2-4 hours. Dosing in children at both 260 mg/m² and 340 mg/m² achieved an AUC similar to the 400 mg and 600 mg daily doses, respectively, in adults. Based on the early findings, the imatinib dose in Study 2108 was selected to be 340 mg/m², and PK/PD analysis confirmed that the 340 mg/m² dose was adequate, with the plasma exposure being similar to that at 600 mg in adults.

Drug-Drug Interactions

CYP3A4 Inhibitors: Substances that inhibit the cytochrome P450 isoenzyme (CYP3A4) activity (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin).may decrease metabolism and increase imatinib concentrations. There is a significant increase in exposure to imatinib (mean C_{max} and AUC increased by 26% and 40%, respectively) when Gleevec is coadministered with ketoconazole (CYP3A4 inhibitor).

CYP3A4 Inducers: Substances that are inducers of CYP3A4 activity may increase metabolism and decrease imatinib plasma concentrations. Co-medications that induce CYP3A4 (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital or St.

John's Wort) may significantly reduce exposure to Gleevec. Pretreatment of healthy volunteers with multiple doses of rifampin followed by a single dose of Gleevec, increased Gleevec oral-dose clearance by 3.8-fold, which significantly ($p < 0.05$) decreased mean C_{max} and $AUC_{(0-\infty)}$. In patients where rifampin or other CYP3A4 inducers are indicated, alternative therapeutic agents with less enzyme induction potential should be considered.

CYP3A4 Substrates: Gleevec increases the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5-fold, respectively, suggesting an inhibition of the CYP3A4 by Gleevec. Particular caution is recommended when administering Gleevec with CYP3A4 substrates that have a narrow therapeutic window (e.g., cyclosporine or pimozide). Gleevec will increase plasma concentration of other CYP3A4 metabolized drugs (e.g., triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.).

Because warfarin is metabolized by CYP2C9 and CYP3A4, patients who require anticoagulation should receive low-molecular weight or standard heparin.

In vitro, Gleevec inhibits the cytochrome P450 isoenzyme CYP2D6 activity at similar concentrations that affect CYP3A4 activity. Systemic exposure to substrates of CYP2D6 is expected to be increased when coadministered with Gleevec. No specific studies have been performed and caution is recommended.

In vitro, Gleevec inhibits acetaminophen O-glucuronidation (K_i value of $58.5 \mu\text{M}$) at therapeutic levels. Systemic exposure to acetaminophen is expected to be increased when coadministered with Gleevec. No specific studies in humans have been performed and caution is recommended.

Enzyme Inhibition: Human liver microsome studies demonstrated that Gleevec is a potent competitive inhibitor of CYP2C9, CYP2D6, and CYP3A4/5 with K_i values of 27, 7.5 and $8 \mu\text{M}$, respectively. Gleevec is likely to increase the blood level of drugs that are substrates of CYP2C9, CYP2D6 and CYP3A4/5.

Special Populations

Pediatric patients

Subject of the current review.

Hepatic Insufficiency: The effect of hepatic impairment on the pharmacokinetics of both imatinib and its major metabolite, CGP74588, was assessed in 84 cancer patients with varying degrees of hepatic impairment (**Table 1**) at imatinib doses ranging from 100-800 mg. Exposure to both imatinib and CGP74588 was comparable between each of the mildly and moderately hepatically-impaired groups and the normal group. However, patients with severe hepatic impairment tend to have higher exposure to both imatinib and its metabolite than patients with normal hepatic function. At steady state, the mean C_{max}/dose and AUC_{24}/dose for imatinib increased by about 63% and 45%, respectively, in patients with severe hepatic impairment

compared to patients with normal hepatic function. The mean C_{max}/dose and AUC₂₄/dose for CGP74588 increased by about 56% and 55%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function.

Table 1: Liver Function Classification

Liver Function Test	Normal (n=14)	Mild (n=30)	Moderate (n=20)	Severe (n=20)
Total Bilirubin	≤ ULN	1.5 ULN	>1.5-3x ULN	>3-10x ULN
SGOT	≤ ULN	> ULN (can be normal if Total Bilirubin is >ULN)	Any	Any

ULN=upper limit of normal for the institution

Renal Insufficiency: No clinical studies were conducted with Gleevec in patients with decreased renal function (studies excluded patients with serum creatinine concentration more than 2 times the upper limit of the normal range). Imatinib and its metabolites are not significantly excreted via the kidney.

Geriatric Use: In the CML clinical studies, approximately 40% of patients were older than 60 years and 10% were older than 70 years. In the study of patients with newly diagnosed CML, 22% of patients were 60 years of age or older. No difference was observed in the safety profile in patients older than 65 years as compared to younger patients, with the exception of a higher frequency of edema. The efficacy of Gleevec was similar in older and younger patients.

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/s/

Martin Cohen

9/8/2006 09:42:39 AM

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-588/s016

Drug name: Gleevec®

Generic name: Imatinib mesylate

Formulation: 100 and 400mg tablets

Pediatric Indication: Treatment of newly diagnosed pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia.

Current Submission: Pediatric supplement

Applicant: Novartis Oncology
One Health Plaza
East Hanover, NJ 07936

OCP Division: Division of Clinical Pharmacology V (HFD-860)

OND Division: Division of Drug Oncology Products (HFD-150)

Submission Dates: 27-March-2006, 06-June-2006, 07-July-2006

Primary Reviewer: Julie M. Bullock, Pharm.D.

**Pharmacometrics
Team Leader:** Joga Gobburu, Ph.D.

Team Leader: Brian Booth, Ph.D.

I. Executive Summary

The sponsor collected intensive pharmacokinetic samples in the phase 1 studies STI571A 0103 and STI571A 03 001, and sparse sampling was gathered in study STI571A 2108. Both phase 1 studies evaluated a range of doses in pediatric patients to obtain a dose that had similar exposure to adults. The phase 2 study, enrolled 53 pediatric patients with newly diagnosed CML at a dose of 340 mg/m²/day. Thirty-three of these patients were included in the pharmacokinetic sparse sampling. With the completion of the three trials above the applicant has met the requirements of the Pediatric Written Request.

The results of the intensive PK sampling in studies 0103 and 03 001 indicate that the pharmacokinetics in pediatrics in adults are similar based on similar values for clearance (pediatrics $6.38 \pm 48\%$ L/hr/m², adult $5.78 \pm 32\%$ L/hr/m²). Sparse samples were collected in the Phase 2 study and were analyzed using a one-compartment model previously developed for adult patients. Briefly, the pharmacokinetic parameters estimated from the model were comparable to those found in previous studies with pediatric patients with intensive PK sampling.

No significant relationships were found between measures of Gleevec exposure and grade 3/4 toxicity.

The incidence of grade 3/4 toxicities was generally less than the incidence of grade 1/2 toxicities for all the common adverse events reported. No significant relationships were found between measures of Gleevec exposure (AUC, average dose, and average dose intensity) and measures of response (cytogenetic and hematologic response) in this population. This may be due to the limited number of patients enrolled and the number of responses that were missing, not assessed, or not available at 3 months when cytogenetic response was assessed.

A. Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the Clinical Pharmacology section of NDA 21-588 and finds it to be acceptable. No labeling changes were made to the clinical pharmacology sections of the label, and no additional changes are being added by OCP.

B. Phase IV Commitments

None.

C. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Sparse samples were collected on the first day of treatment for 33 of the 55 patients enrolled in the Phase 2 study. The pharmacokinetics were evaluated using a one-compartment model with first order elimination which had previously been used to characterize adult pharmacokinetics. The clearance and volume models used body weight (in kg), hemoglobin (Hgb), and white blood cell count (WBC) for covariates as these had previously been found to be significant covariates in the adult models. The C_{max} and AUC estimated from the data in the current submission were similar to those

reported in studies 0103 and 03 001.

The results of the current study also confirmed the findings of the previous review, namely that, the AUC₀₋₂₄ of a 340 mg/m²/day dose in pediatrics provides comparable exposure to the approved adult dose of 400 mg/day.

Exposure response analyses were performed with these data to characterize the relationships between AUC₀₋₂₄ or average daily intensity and effectiveness (cytogenetic response, hematological response) or toxicity. Based on the limited data available, no significant correlation between AUC or dose intensity of Gleevec and the endpoints of effectiveness or toxicity could be concluded.

Julie M. Bullock, Pharm.D.
Clinical Pharmacology Reviewer
Office of Clinical Pharmacology
Division of Clinical Pharmacology V

Concurrence:

Brian Booth, Ph.D.
Clinical Pharmacology Team Leader
Office of Clinical Pharmacology
Division of Clinical Pharmacology V

Concurrence:

Joga Gobburu, Ph.D.
Pharmacometrics Team Leader
Office of Clinical Pharmacology
Division of Clinical Pharmacology - Pharmacometrics

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Brian Booth
9/14/2006 04:07:05 PM

**Medical Officer's Review of
Pediatric Exclusivity Request**

NDA: 20,571
Drug: Camptosar (Irinotecan, CPT-11)
Serial no.: SE8- 021-PM
Sponsor: Pfizer Pharmaceuticals
Medical Reviewer: Amna Ibrahim MD
Team Leader: John Johnson MD
Letter date: December 22, 2003

Recommendation:

The Applicant seeks to obtain pediatric exclusivity for irinotecan by submitting study reports in response to a written request. The Applicant has met all the requirements of the written request, except that children younger than one year were not enrolled. This was discussed at the pediatric exclusivity board and was found to be acceptable.

In the Study P9761, 16% (n=3) responses were observed in the Rhabdomyosarcoma subgroup (n=19). The numbers of patients in this stratum are too small to allow definitive conclusions. In the second phase 2 study, D9802, 9 of 21 patients (43%) had a PR as the best response to irinotecan. However, the irinotecan window was closed to accrual due to 14% early deaths. Although irinotecan demonstrates some promise, no overall efficacy was demonstrated.

No efficacy claim is made. Changes to the label have been proposed by the applicant. These include description of the two phase II studies and safety of study COG 9761. There should be no change in the label as no efficacy has been observed. No unexpected adverse event findings have been noted. Biopharmaceutics review is pending at this time.

Executive Summary:

Four phase 1 and two phase 2 study reports have been submitted to support a response to the written request for pediatric exclusivity. Please see table 1. Three schedules were tested in the phase 1 trials. Two of the phase I studies evaluated daily x 5, q 3 weeks schedule (POG 9571 and P9871). Another studied [daily x 5] x 2, q 3 weeks (St. Judes Study). The last one mimicked the adult schedule of weekly x 4, q 6 weeks (H6957). Daily x 5, q 3 weeks schedule and [daily x 5] x 2, q 3 weeks were studied in two phase II trials.

Three phase I studies and one phase II study were completed. Interim reports have been submitted for two phase I studies (H6957, a phase 1 study and P9761, a phase 2 study). One study (P9871, a phase 1 study) was closed early due to insufficient and slow accrual. DSMB closed the single agent irinotecan window for D9802, a phase 2 study because of the numbers of PD and early death.

Studies H6957 (although patients were enrolled after cut-off date), POG 9571 and St. Judes Studies are adequate for analysis of phase 1 studies. The following observations are made after analyzing the phase I studies:

- Twenty mg/m² [daily x 5] x 2, q 3 weeks evaluated in the St. Judes study appears to be too toxic, although it was thought to be appropriate as a phase 2 dose by the investigator. This high toxicity was again observed in the phase II trial (D9802) that employed this regimen.

- For heavily treated patients in POG9571, 39 mg/m², for less heavily treated patients 50 mg/m² and for children less than 6 years of age 30 mg/m² administered daily x 5 q 3 weeks is an appropriate phase 2 regimen. The 50 mg/m² daily x 5, q 3 regimen was used in phase II study, P9761. The toxicity was acceptable, but the response rate was too low at 5%.

- The investigators of study H6957 concluded that 125 mg/m² of irinotecan is an appropriate phase 2 dose, although by FDA assessment, this dose is too high. It should be noted that 125 mg/m² was initially thought to be the dose for adult patients. In a large NCI trial, an increased number of early deaths were observed at this dose in adult patients.

- P9871 closed early prior to MTD determination.

Two phase II studies were submitted. Conclusions for the phase II studies are as follows:

- P9761 accrued 170 patients and was ongoing at the time of cut-off date. A 5% RR was observed with acceptable toxicity.

- In the other phase II study D9802, single agent irinotecan (SAI) was administered prior to a multi-agent regimen. The SAI window was closed early due to high rate of early disease progressions and deaths.

Two studies were designed to study the interaction of irinotecan with anticonvulsants (AC). One of them was H6957. The 3rd stratum of this study which was designed to evaluate interaction with anticonvulsants was closed with out accruing any patients. In the second study P9871, a total of 9 patients were accrued to all 3 strata (6 in enzyme-inducing ACs, 1 in valproic acid and 2 in other AC strata). This study was closed early due to slow accrual. The sponsor compared the pharmacokinetics of the EIAC patients to a control group who were not on any anticonvulsants. The control group was from another concurrent study (P9761). The demographics, regimens and pharmacokinetic sampling and analysis methods were comparable between the two studies. In the assessment of the Biopharmaceutics reviewer, Dr. Roshni Ramchandani, the studies appear to fulfill the PK requirements of the Written Request.

Table 1: Summary of results of submitted studies

FDA table

	Schedule	Number enrolled	Study completed	Result
Phase 1 studies				
H6957	weekly x 4, q 6 weeks	16	Interim report. 8 pts. enrolled after cut-off date	MTD of 125 mg/m ² probably too high by FDAs definition for strata 2 & 3.
P9871	daily x 5, q 3 weeks	9	Closed early	Study closed early due to slow accrual
POG9571	daily x 5, q 3 weeks	33	Yes	The MTD for stratum 1 =39 mg/m ² , stratum 2 =50 mg/m ² (<6 years age) stratum 3 = 30 mg/m ²
St. Jude Study	[daily x 5] x 2, q 3 weeks	22	Yes	55% experienced DLT at the starting dose
Phase 2 Studies				
P9761 Refractory pts. <2 prior Rx	50 mg/m ² qd x 5, q 3 weeks	170	3 strata still open	5% RR with acceptable toxicity
D9802 Newly diagnosed rhabdomyosarcoma	20 mg/m ² qd x 5, wks 0 & 1, 3&4	21	Yes	High rate of early PDs and deaths. SAI window closed by DSMB

SAI: single agent irinotecan

The applicant states the following in the summary of the clinical document:

“The results of these phase II studies, confirm that single- agent irinotecan is generally tolerable and provides an early indication of clinical activity in children with refractory tumors (solid tumors or CNS tumors) or with metastatic untreated rhabdomyosarcoma. Combinations of irinotecan with other anticancer drugs are critical for the development of new treatments for the pediatric population.”

However, the applicant states in the proposed label *“The effectiveness of CAMPTOSAR in pediatric patients has not been formally established.”* This reviewer agrees with this preceding statement. A description of PK findings, of the two phase II studies and a table that represents

the adverse events in 170 previously treated patients in the COG 9761 phase 2 study has been included in the proposed package insert. However, because the efficacy of irinotecan has not been demonstrated, and because there is no new, meaningful safety information, no changes should be made to the approved label.

Interim reports from phase I and phase II trials have been submitted instead of final reports. However sufficient numbers of patients were enrolled in the phase I and phase II studies. Other than children over 1 year were enrolled into the studies, instead of over 1 month in age, all conditions of the written request have been met.

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/s/

Amna Ibrahim

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-571 SE8-021

Drug name: CAMPTOSAR

Generic name: Irinotecan

Formulation: 20 mg/ml solution for intravenous injection

Adult Indication: Metastatic carcinoma of the colon or rectum

Pediatric Indication: None

Current Submission: Pediatric Supplement

Applicant: Pfizer (agent for Pharmacia and Upjohn)
235 East 42nd Street
New York NY 10017

OCPB Division: Division of Pharmaceutical Evaluation I (HFD-860)

OND Division: Division of Oncology Drug Products (HFD-150)

Submission Dates: 22-Dec-2003, 13-Feb-2004, 21-Jan-2004, 31-Mar- 2004

Primary Reviewer: Roshni Ramchandani, Ph.D.

**Pharmacometrics
Team Leader:** Joga Gobburu, Ph.D.

Team Leader: Brian Booth, Ph.D.

Type of Submission: NDA-Supplemental

1. Executive Summary

Irinotecan hydrochloride (CPT-11, CAMPTOSAR) is a prodrug derivative of camptothecin, an alkaloid obtained from plants such as the *Camptotheca acuminata* tree. Camptothecins are inhibitors of topoisomerase I.

In June 1996, the Food and Drug Administration (FDA) first approved irinotecan, under subpart H regulations for accelerated approval for the second-line treatment of patients with recurrent or progressive metastatic carcinoma of the colon or rectum. Subsequently, full approval was granted for the second-line treatment of metastatic colorectal cancer in October 1998. In April 2000, the FDA approved the use of irinotecan in combination with 5-FU and leucovorin, for first-line therapy for metastatic colorectal cancer.

The current submission includes phase 1 and phase 2 studies evaluating the safety, effectiveness and pharmacokinetics of irinotecan in pediatric patients with a range of malignancies. Six clinical studies (four phase 1 studies and two phase 2 studies) form the basis for full compliance with the CAMPTOSAR Written Request for Pediatric Studies, issued by the FDA on October 30, 2000. These trials provide information regarding the safety and pharmacokinetics (PK) of irinotecan using 3 different schedules of administration and document the activity of irinotecan in a range of pediatric malignancies. Two of the phase I studies evaluated daily x 5, q 3 weeks schedule (POG 9571 and P9871). Another study evaluated a [daily x 5] x 2, q 3 weeks (St. Jude's Study) Schedule. A fourth study evaluated a schedule similar to the adult schedule of weekly x 4, q 6 weeks (H6957). For the two phase 2 trial the daily x 5, q 3 weeks schedule and [daily x 5] x 2, q 3 weeks were studied. The applicant met the requirements of the written request and Pediatric exclusivity was granted to the applicant on March 11, 2004.

Results of the pharmacokinetic analyses of irinotecan and its metabolites showed considerable variability in peak concentrations (C_{max}) and area under the concentration curve (AUC) following single IV infusions of irinotecan at doses ranging from 50 mg/m² to 125 mg/m². As in adults, irinotecan appears to be metabolized to an active metabolite, SN38 (300 to 1000 fold more active than the parent), via carboxylesterase and to inactive metabolites, APC and NPC, via CYP 3A4. The mean (\pm SD) clearance of irinotecan from 2 studies were 16.2 (\pm 6.7) L/h/m² and 17.3 (\pm 4.6) L/h/m². Concomitant use of enzyme-inducing anticonvulsants (EIAcs) resulted in a significantly lower exposure to SN38, where there was a 67-70% reduction in dose-adjusted C_{max} and AUC in patients receiving EIAcs (n=5) compared to patients who were not receiving any anticonvulsants (n=13), although the data are limited.

Exploratory analysis conducted by the applicant did not show any correlations between irinotecan or SN38 exposure and measures of effectiveness (response rates) or toxicity (incidence of severe diarrhea or neutropenia). Exposure-response analysis of the data across all 6 studies conducted by the reviewer showed a trend for increased incidence of

severe (grade 3 or 4) diarrhea and severe (grade 3 or 4) neutropenia with an increase in exposure (AUC) of SN38 in pediatric solid tumor patients. However, this was not statistically significant. These trends were consistent with data in adult patients. A comprehensive characterization of the exposure-toxicity relationship would be critical in targeting of optimal exposures in future studies.

The phase 2 studies included in this supplemental application did not show effectiveness following irinotecan treatment in children with CNS and non-CNS solid tumors. The applicant is not recommending the use of irinotecan in children, however they would like to include information about the pharmacokinetics and safety of irinotecan in the label. The Office of Clinical Pharmacology and Biopharmaceutics recommends that information on the pharmacokinetics in the pediatric population should be included in the label.

1.1 Recommendations

1. There appears to be a correlation between the incidence of severe (grade 3 or 4) diarrhea and SN38 AUC as well as severe (grade 3 or 4) neutropenia and SN38 AUC. However, this relationship was not statistically significant. Pharmacokinetic data was not collected in the majority of the patients. Knowledge of the exposure-toxicity relationship for irinotecan and SN38 would be critical in targeting optimal exposures (b)(4)-----

2. Genotypic differences in UGT1A1, a phase 2 enzyme involved in the glucuronidation of SN38, can result in a decreased rate of elimination of SN38 leading to elevation of SN38 levels and an increased risk of severe toxicity in patients with the less-efficient isoform. Thus, we recommend that you evaluate the relationship between UGT1A1 genotypes on the exposure of SN38 as well as on toxicity:

(In existing data collected from the phase 2 trial already conducted and/or (b)(4)-----

3. Labeling Changes for Irinotecan (#1)

Current Applicant Label

PRECAUTIONS
Pediatric Use

(b)(4)	-----							
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FDA Proposed Labeling:

The applicant proposed text under the ‘CLINICAL PHARMACOLOGY’ section in the ‘Pharmacokinetics in Special Populations’ subsection under ‘Pediatric’ from lines 117 to 129 in the annotated proposed label, should be deleted.

1.2 Phase IV Commitments

None (not applicable).

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The pharmacokinetics of irinotecan and its metabolites were examined in six studies (four phase 1 and two phase 2 studies) conducted in pediatric solid tumor (including CNS tumors) patients. Results of the PK analyses show considerable variability in peak concentrations and AUC following single IV infusions of irinotecan at doses ranging from 50 mg/m² to 125 mg/m². The PK of irinotecan and SN38 showed substantial inter-patient and intra-patient variability as observed in adults. As in adults, irinotecan appears to be metabolized to an active metabolite, SN38, via carboxylesterase and to inactive metabolites, APC and NPC, via CYP 3A4.

The mean (± SD) clearance of irinotecan from 2 studies (phase 1 study H6957 and phase 2 study P9761) were 16.2 (± 6.7) L/h/m² and 17.3 (± 4.6) L/h/m², and mean elimination

half-life was 3.9 and 4.7 hours, respectively. The clearance of irinotecan was correlated with body size metrics (body weight and body surface area) in pediatric patients, and did not appear to differ between male and female patients or between patients who had been heavily pretreated vs. those who had been less-heavily pretreated prior to irinotecan treatment. Concomitant use of enzyme-inducing anticonvulsants (EIAcs) resulted in a significantly lower exposure to SN38, where there was a 67-70% reduction in dose-adjusted C_{max} and AUC in patients receiving EIAcs (n=5) compared to patients who were not receiving any anticonvulsants (n=13). The significance of this interaction and labeling recommendations for the use of anticonvulsants in combination with irinotecan will be addressed in another supplement (s022) submitted by the applicant.

Exploratory analysis conducted by the applicant did not show any correlations between irinotecan or SN38 exposure and measures of effectiveness (response rates) or toxicity (incidence of severe diarrhea or neutropenia). Exposure-response analysis of the data across all 6 studies conducted by the reviewer also does not indicate a significant correlation between incidence of severe (grade 3 or 4) diarrhea or severe (grade 3 or 4) neutropenia and exposure (AUC) of SN38 in the pediatric solid tumor patients. However, the proportion of pediatric patients with grade 3 and 4 diarrhea as well as grade 3 and 4 neutropenia appears to increase with an increase in SN38 AUC. This is in accordance with data in adult patients. A comprehensive characterization of the exposure-toxicity relationship would be critical in targeting of optimal exposures in future studies. The Agency recommends that the applicant collect PK data, using optimal sparse sampling for an appropriate duration post-dose, to ensure reliable estimation of SN38 AUC in all future studies. The collected data should be analyzed to examine the exposure-response relationship for measures of toxicity of irinotecan.

Roshni Ramchandani, Ph.D.
Clinical Pharmacology Reviewer
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation I

Concurrence:

Brian Booth, Ph.D.
Acting Clinical Pharmacology Team Leader
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation I

Concurrence:

Joga Gobburu, Ph.D.
Pharmacometrics Team Leader
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation I

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/s/

Brian Booth

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of this sNDA supplement N21492\S008 for Eloxatin® (oxaliplatin for injection) to add information from the pediatric cancer trials to the label.

1.2 Recommendation on Postmarketing Actions

No new recommendations. Continue post-marketing surveillance

1.2.1 Risk Management Activity

None

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The oxaliplatin pediatric program consists of 4 studies – 2 Phase 1 studies (ARD5531 and DFI7434) and 2 Phase 2 studies (ARD5021 and ARD5530) involving 159 patients ages 7 months to 22 years with advanced and/or refractory solid tumors. Only 1 partial response was observed in the entire program (1/159, 0.25%).

In a Phase 1-2 study (ARD5531), oxaliplatin was administered as a 2-hour IV infusion on days 1, 8 and 15 every 4 weeks (1 cycle), for a maximum of 6 cycles, to 43 patients with refractory or relapsed malignant solid tumors, mainly neuroblastoma and osteosarcoma. Twenty eight (28) pediatric patients in the Phase I study received oxaliplatin at 6 dose levels starting at 40 mg/m² with escalation to 110 mg/m². The dose limiting toxicity (DLT) was sensory neuropathy at the 110mg/m² dose. Fifteen (15) patients received oxaliplatin at a dose of 90 mg/m² IV in the Phase II portion of the study. At this dose, paresthesia (60%, G3/4: 7%), fever (40%, G3/4: 7%) and thrombocytopenia (40%, G3/4: 27%) were the main adverse events. No responses were observed.

In a second Phase 1 study (DFI7434), oxaliplatin was administered to 26 pediatric patients as a 2-hour IV infusion on day 1 every 3 weeks (1 cycle) at 5 dose levels starting at 100 mg/m² with escalation to 160 mg/m², for a maximum of 6 cycles. In a separate cohort, oxaliplatin 85 mg/m² was administered on day 1 every 2 weeks, for a maximum of 9 doses. Patients had metastatic or unresectable solid tumors mainly neuroblastoma and ganglioneuroblastoma. The DLT was sensory neuropathy at the 160 mg/m² dose. Based on these studies, oxaliplatin 130 mg/m² as a 2-hour IV infusion on day 1 every 3

weeks (1 cycle) was used in subsequent Phase II studies. A dose of 85 mg/m² on day 1 every 2 weeks was also found to be tolerable. No responses were observed

In one Phase 2 study (ARD5021), 43 pediatric patients with recurrent or refractory embryonal CNS tumors received oxaliplatin 130 mg/m² every 3 weeks for a maximum of 12 months in absence of progressive disease or unacceptable toxicity. In patients < 10 kg the oxaliplatin dose used was 4.3 mg/kg. The most common adverse events reported were leukopenia (67%, G3/4: 12%), anemia (65%, G3/4: 5%), thrombocytopenia (65%, G3/4: 26%), vomiting (65%, G3/4: 7%), neutropenia (58%, G3/4: 16%) and sensory neuropathy (40%, G3/4: 5%). One partial response was observed.

In a second Phase 2 study (ARD5530), 47 pediatric patients with recurrent solid tumors, including Ewing sarcoma or peripheral PNET, osteosarcoma, rhabdomyosarcoma and neuroblastoma, received oxaliplatin 130 mg/m² every 3 weeks for a maximum of 12 months or 17 cycles. In patients ≤ 12 months old the oxaliplatin dose used was 4.3 mg/kg. The most common adverse events reported were sensory neuropathy (53%, G3/4: 15%), thrombocytopenia (40%, G3/4: 26%), anemia (40%, G3/4: 15%), vomiting (32%, G3/4: 0%), nausea (30%, G3/4: 2%) and AST increased (26%, G3/4: 4%). No responses were observed.

The pharmacokinetic parameters of ultrafiltrable platinum have been evaluated in 109 pediatric patients during the first cycle. The median clearance in pediatric patients estimated by the population pharmacokinetic analysis was 4.80 L/h. The inter-patient variability of platinum clearance in pediatric cancer patients was 40.9 %. Mean platinum pharmacokinetic parameters in ultrafiltrate were C_{max} of 754 ± 244 ng/mL, AUC₀₋₄₈ of 7520 ± 5070 ng·h/mL and AUC of 8830 ± 1570 ng·h/mL at 85 mg/m² of oxaliplatin and C_{max} of 1100 ± 428 ng/mL, AUC₀₋₄₈ of 9740 ± 2520 ng·h/mL and AUC of 17300 ± 5340 ng·h/mL at 130 mg/m² of oxaliplatin. PK parameters are similar to the ones observed in adults. No PK/PD was done due to low response rate in this population (< 1%)

Thus, oxaliplatin is ineffective in the regimens tested in children with refractory solid tumors, with an objective response rate of 1 out of 159 patients (0.25%)

1.3.2 Efficacy:

Only 1 reported partial response out of 159 patients was observed (< 1% of objective response rate). Thus, it appears that oxaliplatin is ineffective in the regimens tested in children with refractory solid tumors.

1.3.3 Safety:

In general, the safety profile of oxaliplatin in the pediatric population was similar to the one observed in the adult population. A total of 98 deaths were reported in all trials. Two of them occurred during the trial (1 case associated with dehydration and the other due to SVC syndrome) and 13 occurred within 28 days after last dose. All deaths were clearly or likely due to disease progression. This is expected in a population with very advanced and refractory metastatic solid tumors. Assessment of cause of AEs is difficult in this

end-stage population. SAEs occurred in ~ 20 % of patients. SAEs seen in 2 or more patients were: headache, hypersensitivity reactions, convulsions and sensory neuropathy. AEs leading to discontinuations were as follows: 3 cases of thrombocytopenia, 2 cases of hypersensitivity reactions and 1 each: pain, dehydration, bone pain, tumor pain, Horner's syndrome, urinary retention, pleural effusion, respiratory distress, hematoma and 1 SVC occlusion. Most common AEs were leukopenia, thrombocytopenia, anemia, vomiting and sensory neuropathy.

1.3.4 Dosing Regimen and Administration:

Based on study ARD5531, the recommended Phase 2 dose was 90 mg/m² oxaliplatin administered IV over 2 hours. Sixteen patients were treated at this dose in this trial. However, in both Phase 2 trials ARD5021 and ARD5530, the dose was 130 mg/m² oxaliplatin administered IV over 2 hours every 3 weeks. For patients < 10 kg, the dose was 4.3 mg/kg.

1.3.5 Drug-Drug Interactions

None reported in pediatric trials.

1.3.6 Special Populations

These studies were performed in kids, ages 7 months until 21 years of age.

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/s/

John Johnson

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-492 SE8- s008

Drug name: ELOXATIN®

Generic name: Oxaliplatin

Formulation: 50 mg or 100 mg vial of sterile, preservative-free lyophilized powder for reconstitution

Adult Indication: Metastatic carcinoma of the colon or rectum

Pediatric Indication: None

Current Submission: Pediatric Supplement

Applicant: Sanofi-Aventis US Inc.
300 Somerset Corporate Boulevard
Bridgewater, NJ 08807

OCP Division: Division of Clinical Pharmacology 5 (HFD-860)

OODP Division: Division of Drug Oncology Products (HFD-150)

Submission Dates: 10-July-2006

Primary Reviewer: Roshni Ramchandani, Ph.D.

**Pharmacometrics
Team Leader:** Joga Gobburu, Ph.D.

Team Leader: Brian Booth, Ph.D.

Type of Submission: NDA-Supplement

(b) (4)

Information that is deleted, it is indicated by a strikethrough. New text is indicated in green text.

Agency's Proposed Labeling:

Under sections:

- FULL PRESCRIBING INFORMATION:CONTENTS
- 8. USE IN SPECIFIC POPULATIONS
- 8.4 Pediatric Use

The pharmacokinetic parameters of ultrafiltrable platinum have been evaluated in (b) (4) 5 pediatric patients during the first cycle. The average clearance in pediatric patients estimated by the population pharmacokinetic analysis was (b) (4) 4.7 L/h/m^2 . The inter-patient variability of platinum clearance in pediatric cancer patients was (b) (4) 1%.

Mean platinum pharmacokinetic parameters in ultrafiltrate were C_{\max} of (b) (4) (b) (4) $0.75 \pm 0.24 \text{ } \mu\text{g/mL}$, AUC_{0-48} of (b) (4) $7.52 \pm 5.07 \text{ } \mu\text{g.h/mL}$ and AUC_{inf} of (b) (4) $8.83 \pm 1.57 \text{ } \mu\text{g.h/mL}$ at 85 mg/m^2 of oxaliplatin and C_{\max} of (b) (4) $1.10 \pm 4.28 \text{ } \mu\text{g/mL}$, AUC_{0-48} of (b) (4) $9.74 \pm 2.52 \text{ } \mu\text{g.h/mL}$ and AUC_{inf} of (b) (4) $17.30 \pm 5.34 \text{ } \mu\text{g.h/mL}$ at 130 mg/m^2 of oxaliplatin.

(b) (4)

B. SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

The applicant has conducted two phase 1 studies to characterize the safety and pharmacokinetics (PK) of oxaliplatin in children with advanced solid tumors. Oxaliplatin was given as a single agent in a weekly regimen in one study and an every-3-week regimen in the other study.

The applicant has also conducted two phase 2 studies to characterize the safety, PK and activity of oxaliplatin in patients with advanced CNS tumors. Oxaliplatin was given at a dose of 130 mg/m^2 every 3 weeks in both studies.

The PK data from the four studies were combined and a population PK model was developed to describe the PK of oxaliplatin. A three-compartment model, with inter-individual variability on CL, V2 and V3 and with a proportional residual error model, described platinum concentrations in plasma ultrafiltrate (PUF) collected in pediatric cancer patients. Inter-individual variability of PUF platinum clearance was significantly related to body weight and glomerular filtration rate. The residual variability for the final model was 41%.

Oxaliplatin exposures seen in pediatric and adult patients were comparable both in plasma and PUF, following comparable doses of 130 mg/m². This suggests that the PK parameters for pediatric and adult patients are comparable. The population mean oxaliplatin clearance in pediatric patients is 5.1 L/hr or 4.7 L/hr/m² (%CV=41%) when normalized for body surface area (BSA). The estimate of oxaliplatin clearance in adults is reported to be 9.3 L/hr at 130 mg/m². Using a nominal BSA of 1.73 m², these clearances would translate to 5.4 L/hr/m². These estimates indicate that the PK in pediatric patients can be predicted from adults.

The sponsor also conducted an exposure-response analysis to examine the relationship between exposure and incidence of various toxicities associated with oxaliplatin, including neutropenia, thrombocytopenia, GI toxicities (nausea, vomiting, diarrhea) and CNS toxicities (peripheral neuropathy). An analysis conducted in patients with exposure (AUC) data did not reveal any significant association between incidence of severe (grade 3/4) toxicity and exposure across studies.

Roshni Ramchandani, Ph.D.
Clinical Pharmacology Reviewer
Office of Clinical Pharmacology
Division Clinical Pharmacology V

Concurrence:

Brian Booth, Ph.D.
Acting Clinical Pharmacology Team Leader
Office of Clinical Pharmacology
Division of Clinical Pharmacology V

Concurrence:

Joga Gobburu, Ph.D.
Pharmacometrics Team Leader
Office of Clinical Pharmacology

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Brian Booth
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CLINICAL REVIEW

Executive Summary Section

Clinical Review for NDA 21-029

Executive Summary

This multidisciplinary medical-statistical review addresses a supplement to NDA 21-029/S-005 for use of Temodar for the treatment of pediatric patients with recurrent malignant brain tumors.

The current supplement presents the results of two Phase 1 and one Phase 2, open-label, multicenter studies of Temodar administered to this patient population. Phase 1 Study I93-125 was a dose escalation study in 27 pediatric patients with advanced non-CNS and CNS cancers. Phase 1 Study I93-125 Extended was actually a Phase 2 Study in 63 pediatric patients with recurrent brain stem glioma and high grade astrocytoma.

Phase 2 study H97-017 was a Cooperative Group-Sponsored Study in 122 pediatric patients with various recurrent CNS tumors. The primary objective for the Phase 2 study was assessment of the response rate of Temodar in patients with recurrent CNS tumors.

Submission of results of these studies meets the FDA Written Request for pediatric studies. On this basis Pediatric Exclusivity has been granted.

In this application it is not completely clear whether the sponsor is making any specific efficacy claims. Labeling changes proposed by Schering-Plough include the addition of pharmacokinetics data, dosage information, and results from the clinical studies in children (efficacy and safety data).

TEMODAR is approved by the FDA for “the treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine.”

I. Recommendations

A. Recommendation on Approvability

The Supplemental Application can be approved, providing the Applicant agrees with the FDA’s proposed labeling revisions. Otherwise the Supplemental Application is approvable, pending the required labeling revisions.

No indication for use in children will be added to the label. No dosage information, pharmacokinetic data or efficacy data from the clinical studies in children will be added to the label. To do so would imply a pediatric use where efficacy for a pediatric use has not been demonstrated. Safety results from the clinical studies in children will be added

CLINICAL REVIEW

Executive Summary Section

to the Pediatric subsection of the PRECAUTIONS section of the label.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

In the absence of clinical efficacy, there are no recommended Phase 4 studies of the use of Temodar in pediatric patients with recurrent brain tumors.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Temozolomide (TEMODAR) Capsules was granted marketing accelerated approval in the United States (NDA 21-029) for treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine. Approval was based on the complete response rate and duration in a single-arm, multicenter study.

The primary source for this sNDA review consisted of data submitted to the original NDA 21-029 from Phase 1 Study 193-125 in pediatric patients with advanced cancers, and previously unsubmitted Phase 1 Study 193-125/Extended study of Temozolomide in pediatric patients with recurrent cancers, and previously unsubmitted Phase 2 Study H97-017 in children and adolescents with recurrent CNS tumors.

It is not completely clear whether this submission makes specific efficacy claims. SPRI proposes labeling changes including an addition of pharmacokinetics data, dosage information, and results from the clinical studies in children (efficacy and safety data) in the Clinical Studies Section of the labeling.

B. Efficacy

Temodar Capsules have been studied in 2 open-label Phase 1 Studies (Study 193-125 and Study 193-125/Extended), and Phase 2 Study H97-017 in children and adolescents with recurrent non-CNS and CNS tumors. The primary endpoint for the Phase 2 Study and for the Extended Phase 1 Study was tumor response rate. Assessment of the response was a secondary endpoint for the initial Phase 1 Study.

The analysis of efficacy showed that in the Study 193-125 there were only one confirmed complete response and three partial responses among 27 patients with advanced non-CNS and CNS cancers.

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In Study 193-125 Extended in 63 patients with recurrent CNS tumors the response rates were 0% complete response, 0% partial response, and 0% complete response and 12% partial response in BSG and HGA population, respectively.

In Phase 2 Study H97-017 in 122 children with recurrent CNS tumors the overall response rate (CR+PR) was 5%. Only one patient achieved CR, and 5 patients had PR's.

C. Safety

Safety was assessed at a doses of 100-240mg/m² daily for 5 days every 28 days, in 204 pediatric patients with recurrent primary brain tumors and some non-CNS tumors. The toxicity profile in children was similar to that of the adult patients. The most common adverse events were dizziness, neuropathy, paresthesia, nausea, vomiting and constipation.

D. Dosing

Study 193-125 Dose Escalation Part.

Twenty seven pediatric patients with advanced cancers, most with primary CNS tumors (high-grade astrocytoma or brain stem glioma), participated in this study. The ages of the patients ranged from 3 to 17 years, with the majority of the patients between 6 and 12 years of age. Patients were stratified for previous treatment with either nitrosurea therapy or craniospinal irradiation (poor risk) versus no such previous treatment (good risk). Patients were randomized to one of the Temodar dose levels (100, 120, 160 or 240mg/m²) given daily for 5 days every 28 days.

Study 193-125 /Extended.

In Extension Part of Study 193-125, 63 pediatric patients with recurrent CNS tumors (brain stem glioma or high-grade astrocytoma) received Temodar daily for 5 days every 28 days. The ages of the patients ranged from 4 to 15 years. Patients were given either 160mg/m²/day if they had prior therapy, or 200mg/m²/day if no prior therapy was received.

Study H97-017.

One hundred twenty two pediatric patients with recurrent CNS tumors (113 patients), and tumor histology categorized by the sponsor as "Other" (9 patients) were enrolled in this Phase 2 Study. Category "other" includes: neuroblastoma, osteosarcoma, Ewing's sarcoma, malignant meningioma, and alveolar soft part sarcoma.

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The ages of the patients ranged from 1 to 23 years. Temodar was administered at the dose of 180mg/m²/day to patients previously treated with cranio-spinal irradiation, and 200mg/m²/day to patients who did not receive radiation treatment.

E. Special Populations

Both Phase 1 Studies (Study 193-125 and Study 193-125 Extended) and Phase 2 Study H97-017 were conducted solely in children and adolescents with recurrent CNS tumors and a few non-CNS tumors. Patients range in age from 1 to 23 years old. The majority of patients were between 3 to 17 years.

CLINICAL REVIEW

Executive Summary Section

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/s/

Alla Shapiro

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Clinical Pharmacology and Biopharmaceutics Review

NDA	21,029/SE8-005
Date of Submission	September 12, 2002
Drug Name	Temodar
Generic	temozolomide
Dosage Form	oral capsule
Strength	5, 20, 100, 250 mg
Sponsor	Schering Corporation 2000 Galloping Hill Road Kenilworth, NJ 07033
Reviewer	Anne Zajicek, M.D., Pharm.D.
Team Leader	N.A.M. Atiqur Rahman
Type of Submission	NDA-Supplement

Executive Summary: Temozolomide is an oral alkylating agent which was approved in 1999 for treatment of adults with refractory anaplastic astrocytoma. A written request was issued for a pediatric study by the Food and Drug Administration on Jan 25, 2001 and amended on August 24, 2001. Three studies are submitted in response to the written request; the Clinical Pharmacology and Biopharmaceutics section of the application was previously submitted with the original NDA. Nineteen children, age 3-17 years with primary brain tumors, were randomized to temozolomide 100, 120, 160, 200 or 240 mg/m² taken orally daily for five days. Pharmacokinetic sampling took place on day 5. Results showed maximum concentration (C_{max}) and area under the concentration time curve (AUC) to be somewhat higher in children than in adults given the same dose, indicating either increased bioavailability or lower clearance in children; these results, however, are difficult to interpret due to the small numbers of patients studied. There was proportionality between dose and area under the concentration-time curve, and there was no apparent relationship between clearance and age.

Comments: The previously submitted pediatric pharmacokinetic study is adequate for the purposes of the written request and the Clinical Pharmacology and Biopharmaceutics review. The remaining question is how very young children took the oral capsule formulation. In future submissions, we recommend plasma MTIC concentration measurements, since it is the active species.

Anne Zajicek, M.D, Pharm.D,
Clinical Pharmacology Reviewer

N.A.M. Atiqur Rahman, Ph.D.
Team Leader

CC: NDA 22,029/SE8-005

HFD-150/ Division File

HFD-150/JohnsonJ,Farella, ShapiroA

HFD-860/MehtaM, SahajwallaC, RahmanNAM, ZajicekA, LazorJ, SelenA, MarroumP

CDR/Biopharm

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/s/

Atiqur Rahman

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Clinical Review of Labeling Supplement with Clinical Data

Application Number: N20671

Supplement Number: 010

Product: Hycamtin (topotecan)

Sponsor: GlaxoSmithKline

Primary Reviewer: Steven Hirschfeld, MD PhD

Secondary Reviewer: John R. Johnson, MD

Date Review Completed: February 21, 2003

Executive Summary: The Food and Drug Administration issued a Pediatric Written Request to GlaxoSmithKline on May 16, 2000 for pediatric studies using Hycamtin (topotecan). The requested studies were for a Phase I dose finding study with pharmacokinetics in at least 18 patients and Phase II or pilot studies in pediatric patients with relapsed or refractory malignancies with at least 14 patients in various tumor types. The sponsor requested an extension of the time to submit the final study reports and this was granted in the form of a revised Written Request that was issued on January 10, 2002 extending the deadline to August 31, 2002. On August 30, 2002 the final study reports in the form of a labeling supplement with clinical data were submitted.

The study reports consisted of summaries of studies previously performed by the Pediatric Oncology Group that were initiated in 1992 and 1993 but were never submitted to the FDA. GlaxoSmithKline obtained the datasets and prepared a study report. The results were that the pediatric Phase II dose was determined that was different from the approved adult dose for topotecan. The Phase II dose for pediatric patients with solid tumors on a schedule of a daily infusion for 5 consecutive days every 21 days was $1.4 \text{ mg/m}^2/\text{d}$ without Granulocyte-Colony Stimulating Factor (G-CSF) and $2.0 \text{ mg/m}^2/\text{d}$ with G-CSF. Doses up to $5.2 \text{ mg/m}^2/\text{d}$ were tolerated in pediatric patients with leukemia. The approved adult dose is $1.5 \text{ mg/m}^2/\text{d}$ for relapsed ovarian cancer or limited disease small cell lung cancer.

The Phase II study in pediatric solid tumors enrolled 108 patients less than 16 years old. The endpoint was response rate. Four tumor types, Ewing's sarcoma/Peripheral Neuroectodermal Tumor, Neuroblastoma, Osteoblastoma, and Rhabdomyosarcoma, had at least 14 patients enrolled. Of the 108 patients enrolled, 93 (86%) died with 11 patients (10%) dying within 30 days of the last dose of topotecan. Eight of the patients that died within 30 days died of progressive disease and 3 died with infection, a known complication of topotecan therapy. Forty-seven patients (44%) were hospitalized for adverse events, primarily febrile neutropenia, fever, or sepsis. The overall response rate was about 8% but in neuroblastoma patients the response rate was 18%. No patient less than 2 years old had a response.

Pediatric Exclusivity was granted on November 20, 2002 because the terms of the Written Request were fairly met. The submitted data are inadequate to independently support an indication and are in diseases that are different than the approved adult indications, therefore, extrapolation cannot be used to support a pediatric indication. If just the dosing information were to be included in the product label, pediatric use may be implied; however, safety and efficacy have not been demonstrated in pediatric cancer patients. The response data are preliminary and further studies would be required and the results would need to be submitted to the FDA and reviewed before pediatric use could be established. Response rates reported for alternative regimens using combinations of available drugs in patients with relapsed neuroblastoma are between 35 and 50%.

For these reasons the pediatric information regarding topotecan should not be incorporated into the product label.

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Steven Hirschfeld
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Clinical Pharmacology and Biopharmaceutics Executive Summary

NDA	20,671/SE8 010
Drug Name	Hycamtin
Generic Name	topotecan
Date of Submission	August 29, 2002
Dosage form	4 mg/vial or 5 mg/vial lyophilized powder for injection
Route of administration	IV Injection
Sponsor	GlaxoSmithKline 1250 South Collegeville Rd Collegeville, PA 19426-0989
Reviewer	Anne Zajicek, M.D., Pharm.D.
Team Leader	N.A.M. Atiqur Rahman, Ph.D.
Pharmacometrics Reviewer	Carl-Michael Staschen, M.D.
Pharmacometrics Team Leader	Joga Gobburu, Ph.D.
Submission Type	NDA-Supplement

I. Executive Summary

The sponsor has submitted three pediatric studies in response to a written request by the FDA. There are two Phase 1 studies, one in children with leukemias and one in children with a variety refractory solid tumors, and one Phase 2 study in patients with various tumor types.

The Phase 1 study in children with leukemia (9275L) enrolled 14 patients, and the study for children with solid tumors (9275) enrolled 36 patients. Pharmacokinetic studies were performed, and the blood was assayed for both lactone (active) and total topotecan concentrations. Results showed similar pharmacokinetic parameters across age groups from 2-16 years. These parameters include (mean \pm standard deviation) clearance of 8.02 ± 3.32 L/hr/m², steady-state volume of distribution of 32.64 ± 12.37 L/m², and half-life of 4.19 ± 1.62 hr. These parameters were similar to reported adult values. No pharmacokinetic-pharmacodynamic relationship for drug exposure and nadir of the white blood cell (WBC) count, as there was maximal suppression of the WBC at the lowest dose.

The pharmacokinetic parameters presented by the applicant were derived from a Bayesian analysis. The applicant has not provided adequate supporting data for the prior pharmacokinetic estimates used in the analysis; therefore, the analysis could not be verified.

No labeling changes for pediatric indications or dosing will be made at this time due to inadequate efficacy data generated in the preliminary Phase 2 study report.

Anne Zajicek, M.D, Pharm.D.
Clinical Pharmacology Reviewer
DPE 1

N.A.M. Atiqur Rahman, Ph.D.
Team Leader
DPE 1

CC: NDA 20,671/SE8 010

HFD-150/ Division File

HFD-150/HirschfeldS

HFD-860/MehtaM, SahajwallaC, RahmanNAM, GobburuJ, StaschenCM,ZajicekA

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Anne Zajicek
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Atiqur Rahman
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**Pediatric Oncology Subcommittee
of the Oncologic Drugs Advisory Committee (ODAC)
June 27, 2007**

**FDA Briefing Document
Session 1: Item 5**

Safety Reporting

Drugs Granted Pediatric Exclusivity

Listed below are the drugs granted pediatric exclusivity which have had a report on adverse events presented to the Pediatric Advisory Committee as mandated under Section 17 of the BPCA.

Drug	Date Exclusivity Granted	Date Reported to Advisory Committee	Pediatric Advisory Committee Outcomes
Busulfex (busulfan)	3-12-02	10-29-03	October 29, 2003 Committee recommended return to routine monitoring for adverse events (AEs) in all populations.
Navelbine (vinorelbine)	8-15-02	2-3-04	February 3, 2004 Committee recommended return to routine monitoring for adverse events (AEs) in all populations.
Hycamtin (topotecan)	11-20-02	6-9-04	June 9, 2004 Committee recommended return to routine monitoring for adverse events (AEs) in all populations.
Temodar (temozolomide)	11-20-02	6-9-04	June 9, 2004 Committee recommended return to routine monitoring for adverse events (AEs) in all populations.
Fludara (fludarabine)	4-03-03	9-15-04	September 15, 2004 Committee recommended return to routine monitoring for adverse events (AEs) in all populations.
Paraplatin (carboplatin)	4-30-04	11-18-05	November 18, 2005 Committee recommended return to routine monitoring for adverse events (AEs) in all populations.
Camptosar (irinotecan)	3-10-04	11-18-05	November 18, 2005 Committee recommended return to routine monitoring for adverse events (AEs) in all populations.
Clolar (clofarabine)	3-30-04	3-22-06	March 22, 2006 Committee recommended return to routine monitoring for AE in all populations.
Gemzar (gemcitabine)	01-27-05	11-16-06	November 16, 2006 Committee recommended return to routine monitoring for adverse events (AEs) in all populations.

**Pediatric Oncology Subcommittee
of the Oncologic Drugs Advisory Committee (ODAC)
June 27, 2007**

FDA Briefing Document

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 - a. 2002 Best Pharmaceuticals for Children Act (BPCA) – Section 2 and 3, pages 1- 4 (also available at: <http://www.fda.gov/cder/pediatric/PL107-109.pdf>) [17p]
 - b. BPCA Draft Slide Presentation for June 2007 Pediatric Subcommittee of the Oncologic Drugs Advisory Committee Meeting
 - A. Zajicek, M.D., Pharm.D; National Institute of Child Health and Human Development/National Institutes of Health (NICHD/NIH). “The Best Pharmaceuticals for Children Act” [20 slides]
 - c. Table 1: Current Status of Drugs Which Have Been Listed by NIH (NICHD) for BPCA - As of March 28, 2007 [5p]
- 2. Bibliography**

**Pediatric Oncology Subcommittee
of the
Oncologic Drugs Advisory Committee
June 27, 2007**

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One Hundred Seventh Congress
of the
United States of America

AT THE FIRST SESSION

*Begun and held at the City of Washington on Wednesday,
the third day of January, two thousand and one*

An Act

To amend the Federal Food, Drug, and Cosmetic Act to improve the safety and efficacy of pharmaceuticals for children.

*Be it enacted by the Senate and House of Representatives of
the United States of America in Congress assembled,*

SECTION 1. SHORT TITLE.

This Act may be cited as the “Best Pharmaceuticals for Children Act”.

SEC. 2. PEDIATRIC STUDIES OF ALREADY-MARKETED DRUGS.

Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) is amended—

- (1) by striking subsection (b); and
- (2) in subsection (c)—

(A) by inserting after “the Secretary” the following: “determines that information relating to the use of an approved drug in the pediatric population may produce health benefits in that population and”; and

(B) by striking “concerning a drug identified in the list described in subsection (b)”.

SEC. 3. RESEARCH FUND FOR THE STUDY OF DRUGS.

Part B of title IV of the Public Health Service Act (42 U.S.C. 284 et seq.) is amended—

- (1) by redesignating the second section 409C, relating to clinical research (42 U.S.C. 284k), as section 409G;
- (2) by redesignating the second section 409D, relating to enhancement awards (42 U.S.C. 284l), as section 409H; and
- (3) by adding at the end the following:

“SEC. 409I. PROGRAM FOR PEDIATRIC STUDIES OF DRUGS.

“(a) LIST OF DRUGS FOR WHICH PEDIATRIC STUDIES ARE NEEDED.—

“(1) IN GENERAL.—Not later than one year after the date of enactment of this section, the Secretary, acting through the Director of the National Institutes of Health and in consultation with the Commissioner of Food and Drugs and experts in pediatric research, shall develop, prioritize, and publish an annual list of approved drugs for which—

“(A)(i) there is an approved application under section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j));

“(ii) there is a submitted application that could be approved under the criteria of section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j));

“(iii) there is no patent protection or market exclusivity protection under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.); or

“(iv) there is a referral for inclusion on the list under section 505A(d)(4)(C) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(d)(4)(C)); and

“(B) in the case of a drug referred to in clause (i), (ii), or (iii) of subparagraph (A), additional studies are needed to assess the safety and effectiveness of the use of the drug in the pediatric population.

“(2) CONSIDERATION OF AVAILABLE INFORMATION.—In developing and prioritizing the list under paragraph (1), the Secretary shall consider, for each drug on the list—

“(A) the availability of information concerning the safe and effective use of the drug in the pediatric population;

“(B) whether additional information is needed;

“(C) whether new pediatric studies concerning the drug may produce health benefits in the pediatric population; and

“(D) whether reformulation of the drug is necessary.

“(b) CONTRACTS FOR PEDIATRIC STUDIES.—The Secretary shall award contracts to entities that have the expertise to conduct pediatric clinical trials (including qualified universities, hospitals, laboratories, contract research organizations, federally funded programs such as pediatric pharmacology research units, other public or private institutions, or individuals) to enable the entities to conduct pediatric studies concerning one or more drugs identified in the list described in subsection (a).

“(c) PROCESS FOR CONTRACTS AND LABELING CHANGES.—

“(1) WRITTEN REQUEST TO HOLDERS OF APPROVED APPLICATIONS FOR DRUGS LACKING EXCLUSIVITY.—The Commissioner of Food and Drugs, in consultation with the Director of the National Institutes of Health, may issue a written request (which shall include a timeframe for negotiations for an agreement) for pediatric studies concerning a drug identified in the list described in subsection (a)(1)(A) (except clause (iv)) to all holders of an approved application for the drug under section 505 of the Federal Food, Drug, and Cosmetic Act. Such a written request shall be made in a manner equivalent to the manner in which a written request is made under subsection (a) or (b) of section 505A of the Federal Food, Drug, and Cosmetic Act, including with respect to information provided on the pediatric studies to be conducted pursuant to the request.

“(2) REQUESTS FOR CONTRACT PROPOSALS.—If the Commissioner of Food and Drugs does not receive a response to a written request issued under paragraph (1) within 30 days of the date on which a request was issued, or if a referral described in subsection (a)(1)(A)(iv) is made, the Secretary, acting through the Director of the National Institutes of Health and in consultation with the Commissioner of Food and Drugs, shall publish a request for contract proposals to conduct the pediatric studies described in the written request.

“(3) DISQUALIFICATION.—A holder that receives a first right of refusal shall not be entitled to respond to a request for contract proposals under paragraph (2).

“(4) GUIDANCE.—Not later than 270 days after the date of enactment of this section, the Commissioner of Food and

Drugs shall promulgate guidance to establish the process for the submission of responses to written requests under paragraph (1).

“(5) CONTRACTS.—A contract under this section may be awarded only if a proposal for the contract is submitted to the Secretary in such form and manner, and containing such agreements, assurances, and information as the Secretary determines to be necessary to carry out this section.

“(6) REPORTING OF STUDIES.—

“(A) IN GENERAL.—On completion of a pediatric study in accordance with a contract awarded under this section, a report concerning the study shall be submitted to the Director of the National Institutes of Health and the Commissioner of Food and Drugs. The report shall include all data generated in connection with the study.

“(B) AVAILABILITY OF REPORTS.—Each report submitted under subparagraph (A) shall be considered to be in the public domain (subject to section 505A(d)(4)(D) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(d)(4)(D)) and shall be assigned a docket number by the Commissioner of Food and Drugs. An interested person may submit written comments concerning such pediatric studies to the Commissioner of Food and Drugs, and the written comments shall become part of the docket file with respect to each of the drugs.

“(C) ACTION BY COMMISSIONER.—The Commissioner of Food and Drugs shall take appropriate action in response to the reports submitted under subparagraph (A) in accordance with paragraph (7).

“(7) REQUESTS FOR LABELING CHANGE.—During the 180-day period after the date on which a report is submitted under paragraph (6)(A), the Commissioner of Food and Drugs shall—

“(A) review the report and such other data as are available concerning the safe and effective use in the pediatric population of the drug studied;

“(B) negotiate with the holders of approved applications for the drug studied for any labeling changes that the Commissioner of Food and Drugs determines to be appropriate and requests the holders to make; and

“(C)(i) place in the public docket file a copy of the report and of any requested labeling changes; and

“(ii) publish in the Federal Register a summary of the report and a copy of any requested labeling changes.

“(8) DISPUTE RESOLUTION.—

“(A) REFERRAL TO PEDIATRIC ADVISORY SUBCOMMITTEE OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE.—If, not later than the end of the 180-day period specified in paragraph (7), the holder of an approved application for the drug involved does not agree to any labeling change requested by the Commissioner of Food and Drugs under that paragraph, the Commissioner of Food and Drugs shall refer the request to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee.

“(B) ACTION BY THE PEDIATRIC ADVISORY SUBCOMMITTEE OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE.—Not later than 90 days after receiving a referral

under subparagraph (A), the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee shall—

“(i) review the available information on the safe and effective use of the drug in the pediatric population, including study reports submitted under this section; and

“(ii) make a recommendation to the Commissioner of Food and Drugs as to appropriate labeling changes, if any.

“(9) FDA DETERMINATION.—Not later than 30 days after receiving a recommendation from the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee under paragraph (8)(B)(ii) with respect to a drug, the Commissioner of Food and Drugs shall consider the recommendation and, if appropriate, make a request to the holders of approved applications for the drug to make any labeling change that the Commissioner of Food and Drugs determines to be appropriate.

“(10) FAILURE TO AGREE.—If a holder of an approved application for a drug, within 30 days after receiving a request to make a labeling change under paragraph (9), does not agree to make a requested labeling change, the Commissioner may deem the drug to be misbranded under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.).

“(11) NO EFFECT ON AUTHORITY.—Nothing in this subsection limits the authority of the United States to bring an enforcement action under the Federal Food, Drug, and Cosmetic Act when a drug lacks appropriate pediatric labeling. Neither course of action (the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee process or an enforcement action referred to in the preceding sentence) shall preclude, delay, or serve as the basis to stay the other course of action.

“(12) RECOMMENDATION FOR FORMULATION CHANGES.—If a pediatric study completed under public contract indicates that a formulation change is necessary and the Secretary agrees, the Secretary shall send a nonbinding letter of recommendation regarding that change to each holder of an approved application.

“(d) AUTHORIZATION OF APPROPRIATIONS.—

“(1) IN GENERAL.—There are authorized to be appropriated to carry out this section—

“(A) \$200,000,000 for fiscal year 2002; and

“(B) such sums as are necessary for each of the five succeeding fiscal years.

“(2) AVAILABILITY.—Any amount appropriated under paragraph (1) shall remain available to carry out this section until expended.”.

SEC. 4. WRITTEN REQUEST TO HOLDERS OF APPROVED APPLICATIONS FOR DRUGS THAT HAVE MARKET EXCLUSIVITY.

Section 505A(d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(d)) is amended by adding at the end the following:

“(4) WRITTEN REQUEST TO HOLDERS OF APPROVED APPLICATIONS FOR DRUGS THAT HAVE MARKET EXCLUSIVITY.—

“(A) REQUEST AND RESPONSE.—If the Secretary makes a written request for pediatric studies (including neonates, as appropriate) under subsection (c) to the holder of an application approved under section 505(b)(1), the holder, not later than 180 days after receiving the written request, shall respond to the Secretary as to the intention of the holder to act on the request by—

“(i) indicating when the pediatric studies will be initiated, if the holder agrees to the request; or

“(ii) indicating that the holder does not agree to the request.

“(B) NO AGREEMENT TO REQUEST.—

“(i) REFERRAL.—If the holder does not agree to a written request within the time period specified in subparagraph (A), and if the Secretary determines that there is a continuing need for information relating to the use of the drug in the pediatric population (including neonates, as appropriate), the Secretary shall refer the drug to the Foundation for the National Institutes of Health established under section 499 of the Public Health Service Act (42 U.S.C. 290b) (referred to in this paragraph as the ‘Foundation’) for the conduct of the pediatric studies described in the written request.

“(ii) PUBLIC NOTICE.—The Secretary shall give public notice of the name of the drug, the name of the manufacturer, and the indications to be studied made in a referral under clause (i).

“(C) LACK OF FUNDS.—On referral of a drug under subparagraph (B)(i), the Foundation shall issue a proposal to award a grant to conduct the requested studies unless the Foundation certifies to the Secretary, within a time-frame that the Secretary determines is appropriate through guidance, that the Foundation does not have funds available under section 499(j)(9)(B)(i) to conduct the requested studies. If the Foundation so certifies, the Secretary shall refer the drug for inclusion on the list established under section 409I of the Public Health Service Act for the conduct of the studies.

“(D) EFFECT OF SUBSECTION.—Nothing in this subsection (including with respect to referrals from the Secretary to the Foundation) alters or amends section 301(j) of this Act or section 552 of title 5 or section 1905 of title 18, United States Code.

“(E) NO REQUIREMENT TO REFER.—Nothing in this subsection shall be construed to require that every declined written request shall be referred to the Foundation.

“(F) WRITTEN REQUESTS UNDER SUBSECTION (b).—For drugs under subsection (b) for which written requests have not been accepted, if the Secretary determines that there is a continuing need for information relating to the use of the drug in the pediatric population (including neonates, as appropriate), the Secretary shall issue a written request under subsection (c) after the date of approval of the drug.”.

SEC. 5. TIMELY LABELING CHANGES FOR DRUGS GRANTED EXCLUSIVITY; DRUG FEES.

(a) **ELIMINATION OF USER FEE WAIVER FOR PEDIATRIC SUPPLEMENTS.**—Section 736(a)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379h(a)(1)) is amended—

(1) by striking subparagraph (F); and

(2) by redesignating subparagraph (G) as subparagraph (F).

(b) **LABELING CHANGES.**—

(1) **DEFINITION OF PRIORITY SUPPLEMENT.**—Section 201 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321) is amended by adding at the end the following:

“(kk) **PRIORITY SUPPLEMENT.**—The term ‘priority supplement’ means a drug application referred to in section 101(4) of the Food and Drug Administration Modernization Act of 1997 (111 Stat. 2298).”.

(2) **TREATMENT AS PRIORITY SUPPLEMENTS.**—Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) is amended by adding at the end the following:

“(l) **LABELING SUPPLEMENTS.**—

“(1) **PRIORITY STATUS FOR PEDIATRIC SUPPLEMENTS.**—Any supplement to an application under section 505 proposing a labeling change pursuant to a report on a pediatric study under this section—

“(A) shall be considered to be a priority supplement; and

“(B) shall be subject to the performance goals established by the Commissioner for priority drugs.

“(2) **DISPUTE RESOLUTION.**—

“(A) **REQUEST FOR LABELING CHANGE AND FAILURE TO AGREE.**—If the Commissioner determines that an application with respect to which a pediatric study is conducted under this section is approvable and that the only open issue for final action on the application is the reaching of an agreement between the sponsor of the application and the Commissioner on appropriate changes to the labeling for the drug that is the subject of the application, not later than 180 days after the date of submission of the application—

“(i) the Commissioner shall request that the sponsor of the application make any labeling change that the Commissioner determines to be appropriate; and

“(ii) if the sponsor of the application does not agree to make a labeling change requested by the Commissioner, the Commissioner shall refer the matter to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee.

“(B) **ACTION BY THE PEDIATRIC ADVISORY SUBCOMMITTEE OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE.**—Not later than 90 days after receiving a referral under subparagraph (A)(ii), the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee shall—

“(i) review the pediatric study reports; and

“(ii) make a recommendation to the Commissioner concerning appropriate labeling changes, if any.

“(C) CONSIDERATION OF RECOMMENDATIONS.—The Commissioner shall consider the recommendations of the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee and, if appropriate, not later than 30 days after receiving the recommendation, make a request to the sponsor of the application to make any labeling change that the Commissioner determines to be appropriate.

“(D) MISBRANDING.—If the sponsor of the application, within 30 days after receiving a request under subparagraph (C), does not agree to make a labeling change requested by the Commissioner, the Commissioner may deem the drug that is the subject of the application to be misbranded.

“(E) NO EFFECT ON AUTHORITY.—Nothing in this subsection limits the authority of the United States to bring an enforcement action under this Act when a drug lacks appropriate pediatric labeling. Neither course of action (the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee process or an enforcement action referred to in the preceding sentence) shall preclude, delay, or serve as the basis to stay the other course of action.”.

SEC. 6. OFFICE OF PEDIATRIC THERAPEUTICS.

(a) ESTABLISHMENT.—The Secretary of Health and Human Services shall establish an Office of Pediatric Therapeutics within the Food and Drug Administration.

(b) DUTIES.—The Office of Pediatric Therapeutics shall be responsible for coordination and facilitation of all activities of the Food and Drug Administration that may have any effect on a pediatric population or the practice of pediatrics or may in any other way involve pediatric issues.

(c) STAFF.—The staff of the Office of Pediatric Therapeutics shall coordinate with employees of the Department of Health and Human Services who exercise responsibilities relating to pediatric therapeutics and shall include—

(1) one or more additional individuals with expertise concerning ethical issues presented by the conduct of clinical research in the pediatric population; and

(2) one or more additional individuals with expertise in pediatrics as may be necessary to perform the activities described in subsection (b).

SEC. 7. NEONATES.

Section 505A(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(g)) is amended by inserting “(including neonates in appropriate cases)” after “pediatric age groups”.

SEC. 8. SUNSET.

Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) is amended by striking subsection (j) and inserting the following:

“(j) SUNSET.—A drug may not receive any 6-month period under subsection (a) or (c) unless—

“(1) on or before October 1, 2007, the Secretary makes a written request for pediatric studies of the drug;

“(2) on or before October 1, 2007, an application for the drug is accepted for filing under section 505(b); and

“(3) all requirements of this section are met.”.

SEC. 9. DISSEMINATION OF PEDIATRIC INFORMATION.

Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) (as amended by section 5(b)(2)) is amended by adding at the end the following:

“(m) DISSEMINATION OF PEDIATRIC INFORMATION.—

“(1) IN GENERAL.—Not later than 180 days after the date of submission of a report on a pediatric study under this section, the Commissioner shall make available to the public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted for the supplement, including by publication in the Federal Register.

“(2) EFFECT OF SUBSECTION.—Nothing in this subsection alters or amends section 301(j) of this Act or section 552 of title 5 or section 1905 of title 18, United States Code.”.

SEC. 10. CLARIFICATION OF INTERACTION OF PEDIATRIC EXCLUSIVITY UNDER SECTION 505A OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT AND 180-DAY EXCLUSIVITY AWARDED TO AN APPLICANT FOR APPROVAL OF A DRUG UNDER SECTION 505(j) OF THAT ACT.

Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) (as amended by section 9) is amended by adding at the end the following:

“(n) CLARIFICATION OF INTERACTION OF MARKET EXCLUSIVITY UNDER THIS SECTION AND MARKET EXCLUSIVITY AWARDED TO AN APPLICANT FOR APPROVAL OF A DRUG UNDER SECTION 505(j).—If a 180-day period under section 505(j)(5)(B)(iv) overlaps with a 6-month exclusivity period under this section, so that the applicant for approval of a drug under section 505(j) entitled to the 180-day period under that section loses a portion of the 180-day period to which the applicant is entitled for the drug, the 180-day period shall be extended from—

“(1) the date on which the 180-day period would have expired by the number of days of the overlap, if the 180-day period would, but for the application of this subsection, expire after the 6-month exclusivity period; or

“(2) the date on which the 6-month exclusivity period expires, by the number of days of the overlap if the 180-day period would, but for the application of this subsection, expire during the six-month exclusivity period.”.

SEC. 11. PROMPT APPROVAL OF DRUGS UNDER SECTION 505(j) WHEN PEDIATRIC INFORMATION IS ADDED TO LABELING.

(a) IN GENERAL.—Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) (as amended by section 10) is amended by adding at the end the following:

“(o) PROMPT APPROVAL OF DRUGS UNDER SECTION 505(j) WHEN PEDIATRIC INFORMATION IS ADDED TO LABELING.—

“(1) GENERAL RULE.—A drug for which an application has been submitted or approved under section 505(j) shall not be considered ineligible for approval under that section or misbranded under section 502 on the basis that the labeling of the drug omits a pediatric indication or any other aspect of labeling pertaining to pediatric use when the omitted indication

or other aspect is protected by patent or by exclusivity under clause (iii) or (iv) of section 505(j)(5)(D).

“(2) LABELING.—Notwithstanding clauses (iii) and (iv) of section 505(j)(5)(D), the Secretary may require that the labeling of a drug approved under section 505(j) that omits a pediatric indication or other aspect of labeling as described in paragraph (1) include—

“(A) a statement that, because of marketing exclusivity for a manufacturer—

“(i) the drug is not labeled for pediatric use; or

“(ii) in the case of a drug for which there is an additional pediatric use not referred to in paragraph (1), the drug is not labeled for the pediatric use under paragraph (1); and

“(B) a statement of any appropriate pediatric contraindications, warnings, or precautions that the Secretary considers necessary.

“(3) PRESERVATION OF PEDIATRIC EXCLUSIVITY AND OTHER PROVISIONS.—This subsection does not affect—

“(A) the availability or scope of exclusivity under this section;

“(B) the availability or scope of exclusivity under section 505 for pediatric formulations;

“(C) the question of the eligibility for approval of any application under section 505(j) that omits any other conditions of approval entitled to exclusivity under clause (iii) or (iv) of section 505(j)(5)(D); or

“(D) except as expressly provided in paragraphs (1) and (2), the operation of section 505.”

(b) EFFECTIVE DATE.—The amendment made by subsection (a) takes effect on the date of enactment of this Act, including with respect to applications under section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)) that are approved or pending on that date.

SEC. 12. STUDY CONCERNING RESEARCH INVOLVING CHILDREN.

(a) CONTRACT WITH INSTITUTE OF MEDICINE.—The Secretary of Health and Human Services shall enter into a contract with the Institute of Medicine for—

(1) the conduct, in accordance with subsection (b), of a review of—

(A) Federal regulations in effect on the date of the enactment of this Act relating to research involving children;

(B) federally prepared or supported reports relating to research involving children; and

(C) federally supported evidence-based research involving children; and

(2) the submission to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives, not later than two years after the date of enactment of this Act, of a report concerning the review conducted under paragraph (1) that includes recommendations on best practices relating to research involving children.

(b) AREAS OF REVIEW.—In conducting the review under subsection (a)(1), the Institute of Medicine shall consider the following:

(1) The written and oral process of obtaining and defining “assent”, “permission” and “informed consent” with respect to child clinical research participants and the parents, guardians, and the individuals who may serve as the legally authorized representatives of such children (as defined in subpart A of part 46 of title 45, Code of Federal Regulations).

(2) The expectations and comprehension of child research participants and the parents, guardians, or legally authorized representatives of such children, for the direct benefits and risks of the child’s research involvement, particularly in terms of research versus therapeutic treatment.

(3) The definition of “minimal risk” with respect to a healthy child or a child with an illness.

(4) The appropriateness of the regulations applicable to children of differing ages and maturity levels, including regulations relating to legal status.

(5) Whether payment (financial or otherwise) may be provided to a child or his or her parent, guardian, or legally authorized representative for the participation of the child in research, and if so, the amount and type of payment that may be made.

(6) Compliance with the regulations referred to in subsection (a)(1)(A), the monitoring of such compliance (including the role of institutional review boards), and the enforcement actions taken for violations of such regulations.

(7) The unique roles and responsibilities of institutional review boards in reviewing research involving children, including composition of membership on institutional review boards.

(c) **REQUIREMENTS OF EXPERTISE.**—The Institute of Medicine shall conduct the review under subsection (a)(1) and make recommendations under subsection (a)(2) in conjunction with experts in pediatric medicine, pediatric research, and the ethical conduct of research involving children.

SEC. 13. FOUNDATION FOR THE NATIONAL INSTITUTES OF HEALTH.

Section 499 of the Public Health Service Act (42 U.S.C. 290b) is amended—

(1) in subsection (b), by inserting “(including collection of funds for pediatric pharmacologic research)” after “mission”;

(2) in subsection (c)(1)—

(A) by redesignating subparagraph (C) as subparagraph (D); and

(B) by inserting after subparagraph (B) the following:

“(C) A program to collect funds for pediatric pharmacologic research and studies listed by the Secretary pursuant to section 409I(a)(1)(A) of this Act and referred under section 505A(d)(4)(C) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(d)(4)(C)).”;

(3) in subsection (d)—

(A) in paragraph (1)—

(i) in subparagraph (B)—

(I) in clause (ii), by striking “and” at the end;

(II) in clause (iii), by striking the period and inserting “; and”;

(III) by adding at the end the following:

“(iv) the Commissioner of Food and Drugs.”; and

(ii) by striking subparagraph (C) and inserting the following:

“(C) The ex officio members of the Board under subparagraph (B) shall appoint to the Board individuals from among a list of candidates to be provided by the National Academy of Science. Such appointed members shall include—

“(i) representatives of the general biomedical field;

“(ii) representatives of experts in pediatric medicine and research;

“(iii) representatives of the general biobehavioral field, which may include experts in biomedical ethics; and

“(iv) representatives of the general public, which may include representatives of affected industries.”; and

(B) in paragraph (2), by realigning the margin of subparagraph (B) to align with subparagraph (A);

(4) in subsection (k)(9)—

(A) by striking “The Foundation” and inserting the following:

“(A) IN GENERAL.—The Foundation”; and

(B) by adding at the end the following:

“(B) GIFTS, GRANTS, AND OTHER DONATIONS.—

“(i) IN GENERAL.—Gifts, grants, and other donations to the Foundation may be designated for pediatric research and studies on drugs, and funds so designated shall be used solely for grants for research and studies under subsection (c)(1)(C).

“(ii) OTHER GIFTS.—Other gifts, grants, or donations received by the Foundation and not described in clause (i) may also be used to support such pediatric research and studies.

“(iii) REPORT.—The recipient of a grant for research and studies shall agree to provide the Director of the National Institutes of Health and the Commissioner of Food and Drugs, at the conclusion of the research and studies—

“(I) a report describing the results of the research and studies; and

“(II) all data generated in connection with the research and studies.

“(iv) ACTION BY THE COMMISSIONER OF FOOD AND DRUGS.—The Commissioner of Food and Drugs shall take appropriate action in response to a report received under clause (iii) in accordance with paragraphs (7) through (12) of section 4091(c), including negotiating with the holders of approved applications for the drugs studied for any labeling changes that the Commissioner determines to be appropriate and requests the holders to make.

“(C) APPLICABILITY.—Subparagraph (A) does not apply to the program described in subsection (c)(1)(C).”;

(5) by redesignating subsections (f) through (m) as subsections (e) through (l), respectively;

(6) in subsection (h)(11) (as so redesignated), by striking “solicit” and inserting “solicit,”; and

(7) in paragraphs (1) and (2) of subsection (j) (as so redesignated), by striking “(including those developed under subsection (d)(2)(B)(i)(II))” each place it appears.

SEC. 14. PEDIATRIC PHARMACOLOGY ADVISORY COMMITTEE.

(a) **IN GENERAL.**—The Secretary of Health and Human Services shall, under section 222 of the Public Health Service Act (42 U.S.C. 217a), convene and consult an advisory committee on pediatric pharmacology (referred to in this section as the “advisory committee”).

(b) **PURPOSE.**—

(1) **IN GENERAL.**—The advisory committee shall advise and make recommendations to the Secretary, through the Commissioner of Food and Drugs and in consultation with the Director of the National Institutes of Health, on matters relating to pediatric pharmacology.

(2) **MATTERS INCLUDED.**—The matters referred to in paragraph (1) include—

(A) pediatric research conducted under sections 351, 409I, and 499 of the Public Health Service Act and sections 501, 502, 505, and 505A of the Federal Food, Drug, and Cosmetic Act;

(B) identification of research priorities related to pediatric pharmacology and the need for additional treatments of specific pediatric diseases or conditions; and

(C) the ethics, design, and analysis of clinical trials related to pediatric pharmacology.

(c) **COMPOSITION.**—The advisory committee shall include representatives of pediatric health organizations, pediatric researchers, relevant patient and patient-family organizations, and other experts selected by the Secretary.

SEC. 15. PEDIATRIC SUBCOMMITTEE OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE.

(a) **CLARIFICATION OF AUTHORITIES.**—

(1) **IN GENERAL.**—The Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (referred to in this section as the “Subcommittee”), in carrying out the mission of reviewing and evaluating the data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of pediatric cancers, shall—

(A) evaluate and, to the extent practicable, prioritize new and emerging therapeutic alternatives available to treat pediatric cancer;

(B) provide recommendations and guidance to help ensure that children with cancer have timely access to the most promising new cancer therapies; and

(C) advise on ways to improve consistency in the availability of new therapeutic agents.

(2) **MEMBERSHIP.**—

(A) **IN GENERAL.**—The Secretary shall appoint not more than 11 voting members to the Pediatric Subcommittee from the membership of the Pediatric Pharmacology Advisory Committee and the Oncologic Drugs Advisory Committee.

(B) **REQUEST FOR PARTICIPATION.**—The Subcommittee shall request participation of the following members in

the scientific and ethical consideration of topics of pediatric cancer, as necessary:

(i) At least two pediatric oncology specialists from the National Cancer Institute.

(ii) At least four pediatric oncology specialists from—

(I) the Children’s Oncology Group;

(II) other pediatric experts with an established history of conducting clinical trials in children; or

(III) consortia sponsored by the National Cancer Institute, such as the Pediatric Brain Tumor Consortium, the New Approaches to Neuroblastoma Therapy or other pediatric oncology consortia.

(iii) At least two representatives of the pediatric cancer patient and patient-family community.

(iv) One representative of the nursing community.

(v) At least one statistician.

(vi) At least one representative of the pharmaceutical industry.

(b) PRE-CLINICAL MODELS TO EVALUATE PROMISING PEDIATRIC CANCER THERAPIES.—Section 413 of the Public Health Service Act (42 U.S.C. 285a–2) is amended by adding at the end the following:

“(c) PRE-CLINICAL MODELS TO EVALUATE PROMISING PEDIATRIC CANCER THERAPIES.—

“(1) EXPANSION AND COORDINATION OF ACTIVITIES.—The Director of the National Cancer Institute shall expand, intensify, and coordinate the activities of the Institute with respect to research on the development of preclinical models to evaluate which therapies are likely to be effective for treating pediatric cancer.

“(2) COORDINATION WITH OTHER INSTITUTES.—The Director of the Institute shall coordinate the activities under paragraph (1) with similar activities conducted by other national research institutes and agencies of the National Institutes of Health to the extent that those Institutes and agencies have responsibilities that are related to pediatric cancer.”

(c) CLARIFICATION OF AVAILABILITY OF INVESTIGATIONAL NEW DRUGS FOR PEDIATRIC STUDY AND USE.—

(1) AMENDMENT OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.—Section 505(i)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)(1)) is amended—

(A) in subparagraph (B), by striking “and” at the end;

(B) in subparagraph (C), by striking the period at the end and inserting “; and”; and

(C) by adding at the end the following:

“(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) AMENDMENT OF THE PUBLIC HEALTH SERVICE ACT.—Section 402(j)(3)(A) of the Public Health Service Act (42 U.S.C. 282(j)(3)(A)) is amended in the first sentence—

(A) by striking “trial sites, and” and inserting “trial sites,”; and

(B) by striking “in the trial,” and inserting “in the trial, and a description of whether, and through what procedure, the manufacturer or sponsor of the investigation of a new drug will respond to requests for protocol exception, with appropriate safeguards, for single-patient and expanded protocol use of the new drug, particularly in children.”.

(d) REPORT.—Not later than January 31, 2003, the Secretary of Health and Human Services, acting through the Commissioner of Food and Drugs and in consultation with the Director of the National Institutes of Health, shall submit to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives a report on patient access to new therapeutic agents for pediatric cancer, including access to single patient use of new therapeutic agents.

SEC. 16. REPORT ON PEDIATRIC EXCLUSIVITY PROGRAM.

Not later than October 1, 2006, the Comptroller General of the United States, in consultation with the Secretary of Health and Human Services, shall submit to Congress a report that addresses the following issues, using publicly available data or data otherwise available to the Government that may be used and disclosed under applicable law:

(1) The effectiveness of section 505A of the Federal Food, Drug, and Cosmetic Act and section 409I of the Public Health Service Act (as added by this Act) in ensuring that medicines used by children are tested and properly labeled, including—

(A) the number and importance of drugs for children that are being tested as a result of this legislation and the importance for children, health care providers, parents, and others of labeling changes made as a result of such testing;

(B) the number and importance of drugs for children that are not being tested for their use notwithstanding the provisions of this legislation, and possible reasons for the lack of testing; and

(C) the number of drugs for which testing is being done, exclusivity granted, and labeling changes required, including the date pediatric exclusivity is granted and the date labeling changes are made and which labeling changes required the use of the dispute resolution process established pursuant to the amendments made by this Act, together with a description of the outcomes of such process, including a description of the disputes and the recommendations of the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee.

(2) The economic impact of section 505A of the Federal Food, Drug, and Cosmetic Act and section 409I of the Public Health Service Act (as added by this Act), including an estimate of—

(A) the costs to taxpayers in the form of higher expenditures by medicaid and other Government programs;

(B) sales for each drug during the 6-month period for which exclusivity is granted, as attributable to such exclusivity;

(C) costs to consumers and private insurers as a result of any delay in the availability of lower cost generic equivalents of drugs tested and granted exclusivity under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.), and loss of revenue by the generic drug industry and retail pharmacies as a result of any such delay; and

(D) the benefits to the government, to private insurers, and to consumers resulting from decreased health care costs, including—

(i) decreased hospitalizations and fewer medical errors, due to more appropriate and more effective use of medications in children as a result of testing and re-labeling because of the amendments made by this Act;

(ii) direct and indirect benefits associated with fewer physician visits not related to hospitalization;

(iii) benefits to children from missing less time at school and being less affected by chronic illnesses, thereby allowing a better quality of life;

(iv) benefits to consumers from lower health insurance premiums due to lower treatment costs and hospitalization rates; and

(v) benefits to employers from reduced need for employees to care for family members.

(3) The nature and type of studies in children for each drug granted exclusivity under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.), including—

(A) a description of the complexity of the studies;

(B) the number of study sites necessary to obtain appropriate data;

(C) the number of children involved in any clinical studies; and

(D) the estimated cost of each of the studies.

(4) Any recommendations for modifications to the programs established under section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) and section 409I of the Public Health Service Act (as added by section 3) that the Secretary determines to be appropriate, including a detailed rationale for each recommendation.

(5) The increased private and Government-funded pediatric research capability associated with this Act and the amendments made by this Act.

(6) The number of written requests and additional letters of recommendation that the Secretary issues.

(7) The prioritized list of off-patent drugs for which the Secretary issues written requests.

(8)(A) The efforts made by the Secretary to increase the number of studies conducted in the neonate population; and

(B) the results of those efforts, including efforts made to encourage the conduct of appropriate studies in neonates by companies with products that have sufficient safety and other information to make the conduct of studies ethical and safe.

SEC. 17. ADVERSE-EVENT REPORTING.

(a) TOLL-FREE NUMBER IN LABELING.—Not later than one year after the date of the enactment of this Act, the Secretary of Health and Human Services shall promulgate a final rule requiring that

the labeling of each drug for which an application is approved under section 505 of the Federal Food, Drug, and Cosmetic Act (regardless of the date on which approved) include the toll-free number maintained by the Secretary for the purpose of receiving reports of adverse events regarding drugs and a statement that such number is to be used for reporting purposes only, not to receive medical advice. With respect to the final rule:

(1) The rule shall provide for the implementation of such labeling requirement in a manner that the Secretary considers to be most likely to reach the broadest consumer audience.

(2) In promulgating the rule, the Secretary shall seek to minimize the cost of the rule on the pharmacy profession.

(3) The rule shall take effect not later than 60 days after the date on which the rule is promulgated.

(b) DRUGS WITH PEDIATRIC MARKET EXCLUSIVITY.—

(1) IN GENERAL.—During the one year beginning on the date on which a drug receives a period of market exclusivity under 505A of the Federal Food, Drug, and Cosmetic Act, any report of an adverse event regarding the drug that the Secretary of Health and Human Services receives shall be referred to the Office of Pediatric Therapeutics established under section 6 of this Act. In considering the report, the Director of such Office shall provide for the review of the report by the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee, including obtaining any recommendations of such subcommittee regarding whether the Secretary should take action under the Federal Food, Drug, and Cosmetic Act in response to the report.

(2) RULE OF CONSTRUCTION.—Paragraph (1) may not be construed as restricting the authority of the Secretary of Health and Human Services to continue carrying out the activities described in such paragraph regarding a drug after the one-year period described in such paragraph regarding the drug has expired.

SEC. 18. MINORITY CHILDREN AND PEDIATRIC-EXCLUSIVITY PROGRAM.

(a) PROTOCOLS FOR PEDIATRIC STUDIES.—Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) is amended in subsection (d)(2) by inserting after the first sentence the following: “In reaching an agreement regarding written protocols, the Secretary shall take into account adequate representation of children of ethnic and racial minorities.”

(b) STUDY BY GENERAL ACCOUNTING OFFICE.—

(1) IN GENERAL.—The Comptroller General of the United States shall conduct a study for the purpose of determining the following:

(A) The extent to which children of ethnic and racial minorities are adequately represented in studies under section 505A of the Federal Food, Drug, and Cosmetic Act; and to the extent ethnic and racial minorities are not adequately represented, the reasons for such under representation and recommendations to increase such representation.

(B) Whether the Food and Drug Administration has appropriate management systems to monitor the representation of the children of ethnic and racial minorities in such studies.

(C) Whether drugs used to address diseases that disproportionately affect racial and ethnic minorities are being studied for their safety and effectiveness under section 505A of the Federal Food, Drug, and Cosmetic Act.

(2) DATE CERTAIN FOR COMPLETING STUDY.—Not later than January 10, 2003, the Comptroller General shall complete the study required in paragraph (1) and submit to the Congress a report describing the findings of the study.

SEC. 19. TECHNICAL AND CONFORMING AMENDMENTS.

Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) (as amended by sections 2(1), 5(b)(2), 9, 10, 11, and 17) is amended—

(1)(A) by striking “(j)(4)(D)(ii)” each place it appears and inserting “(j)(5)(D)(ii)”;

(B) by striking “(j)(4)(D)” each place it appears and inserting “(j)(5)(D)”;

(C) by striking “505(j)(4)(D)” each place it appears and inserting “505(j)(5)(D)”;

(2) by redesignating subsections (a), (g), (h), (i), (j), (k), (l), (m), (n), and (o) as subsections (b), (a), (g), (h), (n), (m), (i), (j), (k), and (l) respectively;

(3) by moving the subsections so as to appear in alphabetical order;

(4) in paragraphs (1), (2), and (3) of subsection (d), subsection (e), and subsection (m) (as redesignated by paragraph (2)), by striking “subsection (a) or (c)” and inserting “subsection (b) or (c)”;

(5) in subsection (g) (as redesignated by paragraph (2)), by striking “subsection (a) or (b)” and inserting “subsection (b) or (c)”.

Speaker of the House of Representatives.

*Vice President of the United States and
President of the Senate.*

The Best Pharmaceuticals for Children Act

Anne Zajicek, M.D., Pharm.D.

Pediatric Medical Officer

National Institute of Child Health and Human
Development

National Institutes of Health



Best Pharmaceuticals for Children Act

- ◆ Enacted January 2002, exclusivity provision will sunset October 2007
- ◆ Continues exclusivity provision of FDAMA
- ◆ Purpose: pediatric labeling

Pediatric Labeling

- ◆ Pre-approval: Pediatric Research Equity Act
- ◆ On-patent:
 - Best Pharmaceuticals for Children Act which continues the exclusivity provisions of FDAMA
 - Studies supported by the Foundation for the NIH
- ◆ Off-patent: Best Pharmaceuticals for Children Act

Best Pharmaceuticals for Children Act

◆ In pediatric oncology

- prioritize new drugs for study
- assure timely access to new treatments
- develop pre-clinical models of pediatric cancers

Master List of all Off-Patent Drugs
which lack adequate pediatric labeling
N=200

Consider for prioritizing:

- Availability of S/E data
- Are additional data needed?
- Will new studies produce health benefits?
- Reformulation?

Consultation with
experts in pediatric
practice and research

Develop, prioritize, publish an
Annual List
N=5-15

Priority List

- ◆ Developed by NIH

- ◆ In consultation with

- Institutes and Centers of the National Institutes of Health
- Federal Agencies
 - ◆ Food and Drug Administration
 - ◆ Centers for Disease Control and Prevention
- Pediatric subspecialists and subspecialty groups
- Advocacy groups

Drugs on the Priority List: January 2003

FR 68: 13; Jan 21, 2003

- ◆ Azithromycin
- ◆ Baclofen*
- ◆ Bumetanide
- ◆ Dobutamine
- ◆ Dopamine
- ◆ Furosemide
- ◆ Heparin
- ◆ Lithium
- ◆ Lorazepam
- ◆ Rifampin
- ◆ Sodium
nitroprusside
- ◆ Spironolactone

Drugs on the Priority List: August 2003

FR 68: 156; Aug 13, 2003

- ◆ Ampicillin/sulbactam
- ◆ Diazoxide
- ◆ Isoflurane
- ◆ Lindane
- ◆ Meropenem
- ◆ Metoclopramide*
- ◆ Piperacillin/
tazobactam
- ◆ Promethazine

Drugs on the Priority List: February 2004

FR 69:30; February 13, 2004

- ◆ Ampicillin
- ◆ Ketamine
- ◆ Vincristine
- ◆ Actinomycin-D
- ◆ Metolazone

Drugs on the Priority List: January 2005

FR 70:17; January 27, 2005

- ◆ Ivermectin
- ◆ Hydrocortisone valerate
- ◆ Hydrochlorothiazide
- ◆ Ethambutol
- ◆ Griseofulvin
- ◆ Methadone
- ◆ Hydroxychloroquine
- ◆ Sevelamer*
- ◆ Morphine*

Drugs on the Priority List: April 2006

FR 70:79; April 25, 2006

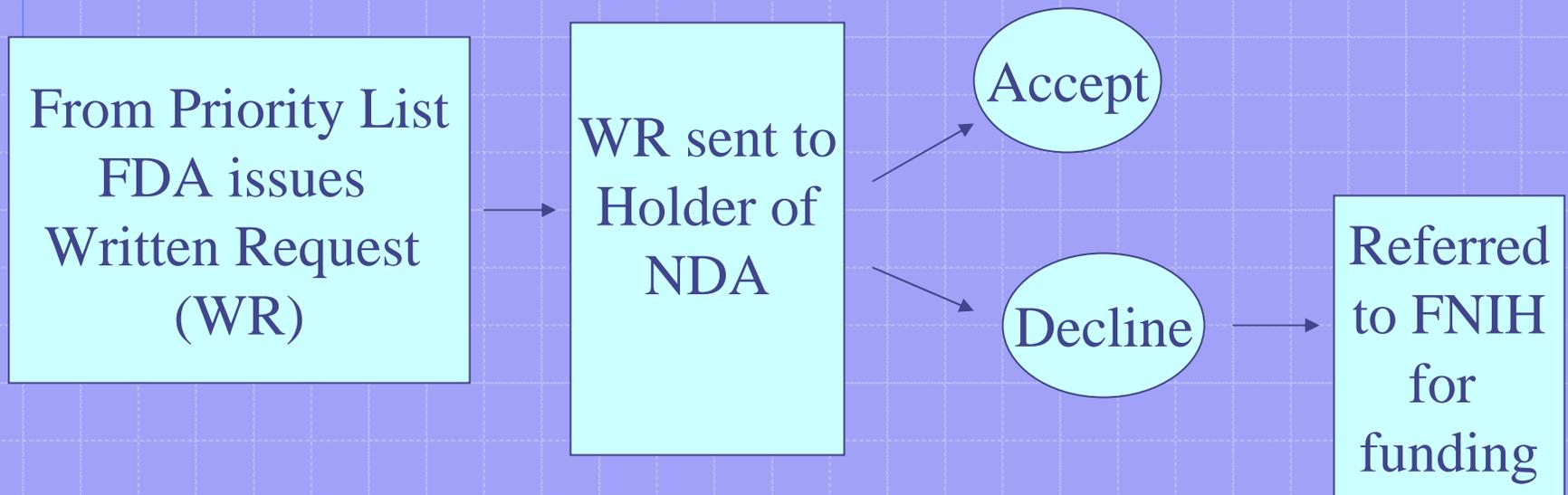
- ◆ ADHD: methylphenidate
- ◆ Hypertension: diuretics
- ◆ Parasitic Diseases: albendazole, mebendazole
- ◆ Influenza: amantidine, rimantidine
- ◆ Cancer: methotrexate, daunomycin
- ◆ Poisonings: pralidoxime
- ◆ Sickle Cell Anemia: hydroxyurea

Drugs on the Priority List: March 2007

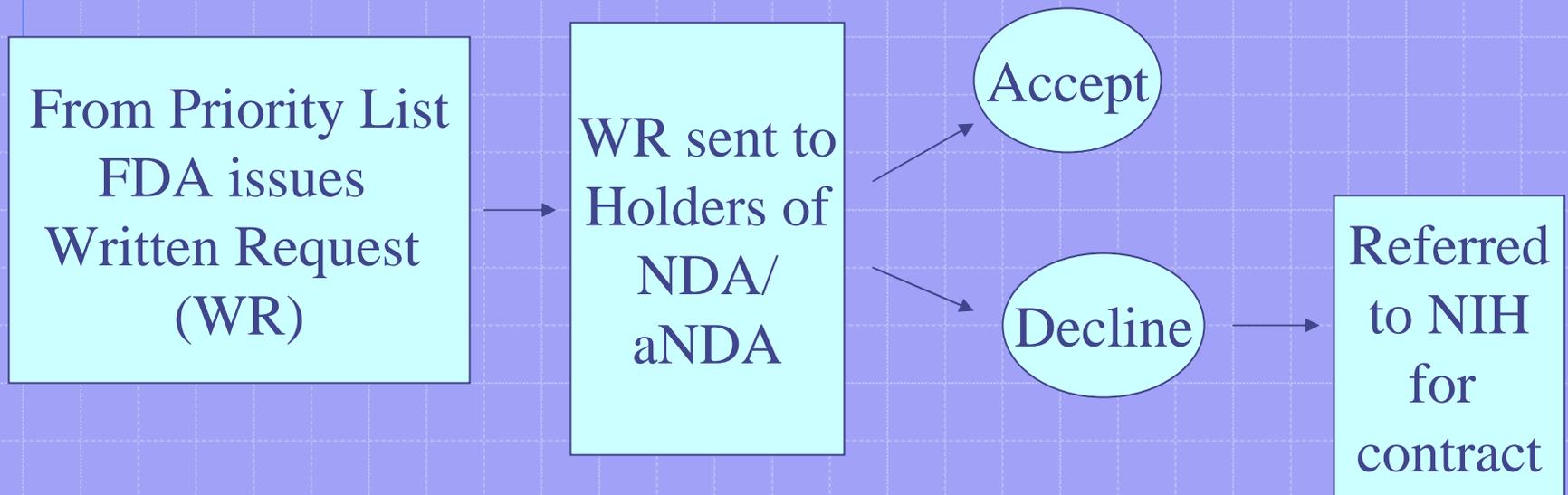
FR 72(59): 14588-89

- ◆ Infectious Diseases: Methicillin-resistant Staph aureus infection
 - Clindamycin, tetracyclines, trimethoprim-sulfamethoxazole
- ◆ Hypertension: clinical trial designs
- ◆ Neonatal Research: clinical trial designs
- ◆ Cancer: Neuroblastoma
 - **13-cis retinoic acid**
- ◆ Asthma: clinical trial designs in young children

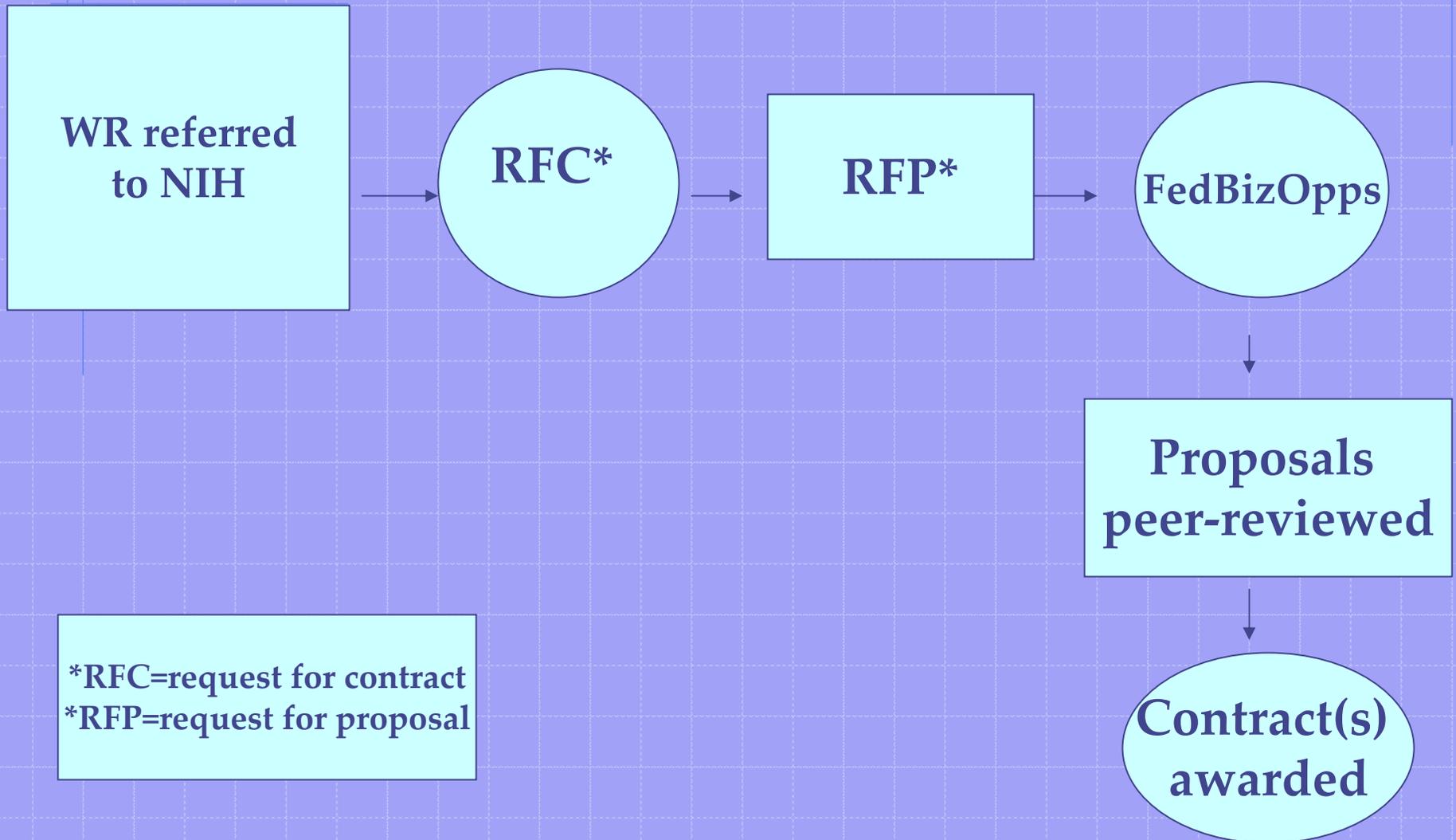
FDA Issues a Written Request: On-Patent



FDA Issues a Written Request: Off-Patent



Contracting Process



Results So Far...



Studies On-Going

- ◆ Lorazepam: Clinical studies for treatment of status epilepticus
 - Study 1: PK
 - Study 2: Efficacy, safety study comparing lorazepam to diazepam
- ◆ Lorazepam: Clinical studies of sedation of children on ventilators in an intensive care unit
- ◆ Nitroprusside: Clinical studies to reduce blood pressure during surgery to reduce blood loss
- ◆ Lithium: Clinical studies to define treatment of mania in children with bipolar disorder
- ◆ Baclofen: Clinical studies of oral baclofen to treat spasticity, most commonly from cerebral palsy

Studies On-Going

- ◆ Vincristine: Studies to evaluate neurotoxicity, PK in children (NCI-COG)
- ◆ Actinomycin-D: Studies to evaluate hepatotoxicity/VOD, PK in children (NCI-COG)
- ◆ Daunomycin: Pharmacokinetics, safety, efficacy of daunomycin to treat childhood cancers and relationship to body weight (NCI-COG)
- ◆ Methotrexate: Clinical studies to evaluate neurocognitive outcomes of pediatric patients with high risk acute lymphoblastic leukemia (NCI-COG)

Studies On-Going

- ◆ Ketamine - Preclinical studies to evaluate the scientific and safety concerns about the use as an anesthetic in children
- ◆ Hydroxyurea- Clinical studies to improve treatment of children with sickle cell disease (NHLBI)
- ◆ Methylphenidate – Preclinical and clinical evaluation of pharmacokinetics and safety to understand reports of cytogenetic toxicity (NIEHS)
- ◆ Morphine – preclinical basic science evaluations of the developmental expression of opioid receptors to better understand management of pain in children of different developmental stages and safety issues in treating pain in neonates

Summary

- ◆ Work in Progress
- ◆ Partnership with FDA
- ◆ NIH responsible for
 - prioritizing list
 - providing input on the Written Request
 - sponsoring clinical studies in children that will improve pediatric therapeutics



**Table 1: Current Status of Drugs Which Have Been Listed by NIH (NICHD) for BPCA
As of March 28, 2007**

Drug	Indication	Listing	Patent Status	Written Request/ RFP	Clinical Trial Primary Site	Current Status and/or Clinical Trial Design
13-Cis-Retinoic Acid	Neuroblastoma	2007	Off-patent	Pending	Pending	Pending
*Acyclovir	Herpetic infections	2005	On-patent	FDA	N/A	Being reviewed for re-labeling based on published literature.
Ampicillin	Infection	2004	Off-patent	NICHD	N/A	RFC under development, data gathering in process.
Ampicillin/sulbactam	Infection	2003	Off-patent	FDA	N/A	Inactive.
Azithromycin (IV)	Prevention of bronchopulmonary dysplasia (BPD) in neonates colonized with Ureaplasma urealyticum	2003	Off-patent	NICHD	N/A	Currently reviewing available scientific data on safety and efficacy.
Azithromycin (PO)	Prevention treatment of Chlamydia conjunctivitis and pneumonia	2003	Off-patent	NICHD	N/A	Memo to file finalized that due to feasibility issues and lack of response to RFP, clinical studies could not be done.
*Baclofen	Oral treatment of spasticity from cerebral palsy	2003	On-patent	NICHD	Washington University of St. Louis	Chart review underway. Pharmacokinetics, safety and efficacy studies to be performed.
Bumetanide	Diuresis	2003	Off-patent	FDA	N/A	Memo to file pending that based on scientific recommendation, studies are not recommended at this time.
*Bupropion	Treatment of Depression	2004	On-patent	FNIH NICHD	N/A	Consultation with scientific community completed. Written Request referred to FNIH.
*Bupropion	Treatment for smoking cessation	2004	On-patent	FNIH NICHD	N/A	Written Request referred to FNIH.
Clindamycin	Methicillin-resistant Staphylococcus aureus infection	2007	Off-patent	Pending	Pending	Pending
Clonidine	Autism	2005	Off-patent	FDA	N/A	Inactive.
Clonidine	Attention deficit disorder	2005	Off-patent	FDA	N/A	Preliminary consultation with scientific community completed and currently reviewing scientific information from a previously performed clinical study.
Cyclosporine	Cardiac transplant rejection	2005	Off-patent	FDA	N/A	Inactive.

Drug	Indication	Listing	Patent Status	Written Request/RFP	Clinical Trial Primary Site	Current Status and/or Clinical Trial Design
D-actinomycin	Cancer	2004	Off-patent	NICHHD	NICHHD Partnership with NCI/COG	NCI/COG studies underway.
Daunomycin	Cancer	2006	Off-patent	NICHHD	NICHHD Partnership with NCI/COG	NCI/COG studies underway.
*Dexrazoxane	Prophylaxis from cardiotoxicity of doxorubicin	2005	On-patent	FNIH NICHHD	N/A	WR referred to FNIH.
Diazoxide	Hypoglycemia	2003	Off-patent	FDA	N/A	Memo to file pending that due feasibility issues, studies not recommended
Dobutamine	Hypotension, low cardiac output in neonates	2003	Off-patent	FDA	N/A	Memo to file pending that due to issues with feasibility and clinical trial design, studies not recommended at this time.
Dopamine	Hypotension, low cardiac output in neonates	2003	Off-patent	FDA	N/A	Memo to file pending that due to issues with feasibility and clinical trial design, studies not recommended at this time.
Doxycycline	Methicillin-resistant Staphylococcus aureus infection	2007	Off-patent	Pending	Pending	Pending
*Eletriptan	Migraine headaches in adolescents	2005	On-patent	FNIH NICHHD	N/A	WR referred to FNIH.
Ethambutol	Tuberculosis	2005	Off-patent	FDA	N/A	Data gathering in process.
Flecainide	Ventricular arrhythmia	2005	Off-patent	FDA	N/A	Data gathering in process.
Furosemide	Diuresis	2003	Off-patent	FDA	N/A	Memo to file pending that based on scientific recommendation, studies are not recommended at this time.
Griseofulvin	Tinea capitis	2005	Off-patent	NICHHD	N/A	RFC under development, data gathering in process.
Heparin	Anticoagulation	2003	Off-patent	FDA		Already labeled for patients \geq 1 kg. Memo to file finalized that no further study recommended.

Drug	Indication	Listing	Patent Status	Written Request/RFP	Clinical Trial Primary Site	Current Status and/or Clinical Trial Design
Hydrochlorothiazide	Hypertension	2005	Off-patent	FDA	N/A	Consultation with scientific community concerning diagnosis and treatment of pediatric hypertension completed and recommendations provided to NICHD/FDA. WR in process.
*Hydrocortisone valerate ointment and cream	Dermatitis	2005	On-patent	FDA	N/A	Inactive.
Hydroxychloroquine	Connective tissue disorders	2005	Off-patent	FDA	N/A	Literature review in process.
*Hydroxyurea	Sickle Cell Disease	2006	On-patent	FNIH NICHD	NICHD Partnership with NHLBI	PK, efficacy and safety studies continue. Participants currently being enrolled.
Isoflurane	Maintenance of general anesthesia	2003	Off-patent	FDA	N/A	Awaiting results of Ketamine preclinical study.
Ivermectin	Scabies	2005	Off-patent	FDA	N/A	Memo to file finalized that formulation issues preclude study.
Ketamine	Sedation	2004	Off-patent	FDA	NICHD Partnership with NCTR, FDA	Pre-clinical toxicology studies underway, results pending.
Lindane	Second line treatment of scabies	2003	Off-patent	FDA	N/A	WR accepted by NDA holder. Results pending.
Lithium	Treatment of mania in bipolar disorder	2003	Off-patent	NICHD	Case Western Reserve University	PK, safety, efficacy, and tolerability studies underway. Participants currently being enrolled.
Lorazepam	Treatment of Status Epilepticus	2003	Off-patent	NICHD	Children's National Medical Center	PK study complete. Follow up study pending community consultation.
Lorazepam	Sedation in the intensive care unit for children on respirators	2003	Off-patent	NICHD	Case Western Reserve University	Pharmacokinetics, safety and efficacy studies continue. Participants are currently being enrolled.
Meropenem	Infection	2003	Off-patent	NICHD	N/A	Currently in contract negotiations.
Methadone	Neonates with opioid withdrawal	2005	Off-patent	FDA	N/A	Data gathering in process.
Methotrexate	Cancer	2006	Off-patent	NICHD	NICHD Partnership with NCI/COG	NCI/COG studies underway.
*Metoclopramide	Gastro-esophageal reflux	2003	On-patent	FNIH NICHD	N/A	WR referred to FNIH.

Drug	Indication	Listing	Patent Status	Written Request/RFP	Clinical Trial Primary Site	Current Status and/or Clinical Trial Design
*Methylphenidate	Attention Deficit and Hyperactivity Disorder	2005	On-patent	NICHHD	NICHHD Partnership with NIEHS, NIMH, FDA/NCTR	Currently under evaluation of genetic toxicity based on published report of cytogenetic effect of Methylphenidate reported in <u>Cancer Letters</u> (2005).
Metolazone	Diuresis	2004	Off-patent	FDA	N/A	Memo to file pending that based on scientific recommendation, studies are not recommended at this time.
*Morphine	Analgesia	2004	On-patent	FNIH NICHHD	Children's National Medical Center	Grant awarded by NICHHD in 2005 for study in neonates and is currently underway.
Piperacillin/tazobactam	Infection	2003	Off-patent	FDA	N/A	Already labeled down to 2 months of age. Memo to file pending that no further study recommended.
Pralidoxime	Organophosphate Poisoning	2006	Off-patent	FDA	N/A	Systematic literature review underway for potential label update.
Promethazine	Nausea and vomiting	2003	Off-patent	FDA	N/A	Currently has black boxed warning. Memo to file pending.
Rifampin	Methicillin-resistant Staphylococcus aureus endocarditis	2003	Off-patent	NICHHD	N/A	Inactive. Frequency of condition being reviewed.
Rifampin	Central nervous system shunt infection	2003	Off-patent	NICHHD	N/A	Inactive. Frequency of condition being reviewed.
*Sevelamer	Hyperphosphatemia in chronic renal failure	2005	On-patent	FNIH NICHHD	N/A	Written Request referred to FNIH.
Sodium nitroprusside	Control of blood pressure	2003	Off-patent	NICHHD	Duke and Stanford Universities	Pharmacokinetics, safety, studies underway. Participants continue to be enrolled.
Spironolactone	Diuresis	2003	Off-patent	FDA	N/A	Memo to file pending that based on scientific recommendation, studies are not recommended at this time.
Tetracycline	Methicillin-resistant Staphylococcus aureus infection	2007	Off-patent	Pending	Pending	Pending
*Trimethoprim-Sulfamethoxazole	Methicillin-resistant Staphylococcus aureus infection	2007	On-patent	Pending	Pending	Pending
Vincristine	Cancer	2004	Off-patent	NICHHD	NICHHD Partnership with NCI/COG	NCI/COG studies underway.

Drug	Indication	Listing	Patent Status	Written Request/ RFP	Clinical Trial Primary Site	Current Status and/or Clinical Trial Design
*Zonisamide	Partial Seizures	2005	On-patent	FNIH NICHD	N/A	Written Request referred to FNIH.

Key: Drug is the generic name, Indication summarizes the indication or condition for which the drug is to be tested, Listing notes the year in which the drug was added to the list for testing, Patent Status is the on or off patent status of the drug, WR indicates a Written Request has been issued by the FDA and denotes where the request for and the processing of information currently resides {FDA, Foundation for NIH (FNIH) or NIH}, Request for Proposals (RFP) indicates the RFP was published by NICHD and its current status, Clinical Trial Primary Site identifies the institution who has received the contract and has designed and implemented the pre-clinical or clinical protocol, Clinical Trial Design indicates in general terms the format of the proposed or actual pre-clinical or clinical trials and the phases of drug development being conducted. N/A refers to a process that is not applicable to a particular drug at this time. Inactive generally refers to feasibility issues that make the formation of the WR or RFP difficult to complete.

NHLBI is the National Heart, Lung, and Blood Institute, NCI is the National Cancer Institute, COG is the Children's Oncology Group, NIEHS is the National Institute of Environmental Health Sciences, NIMH is the National Institute of Mental Health, NCTR is the National Center for Toxicology Research.

*Indicates that a drug is currently on-patent and will be studied under a different funding mechanism than the off-patent process as described in the BPCA Legislation of 2002. For an on-patent drug, if the manufacturer has denied or failed to respond to the WR issued by the FDA in 120 days, the FDA refers the drug to the FNIH and requests that it be considered for FNIH support of pediatric studies. These drugs are also discussed at the annual scientific listing meetings.