IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE TRADEMARK TRIAL AND APPEAL BOARD

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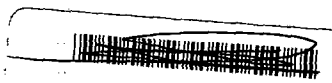
| Alfacell Corporation<br>Petitioner<br>vs.<br>Anticancer, Inc.<br>Registrant | Cancellation No.: 32,202<br>Registration No. 1,987,445 |



04-11-2003
U.S. Patent & TMOfc/TM Mail Rcpt Dt. #39

**REGISTRANT ANTICANCER, INC.'S NOTICE OF RELIANCE: PRINTOUTS FROM WEBSITE OF THE CENTER FOR DRUG EVALUATION AND RESEARCH**

Pursuant to 37 C.F.R. § 2.122(d)(2) and Rule 703.02(a) of the Trademark Trial and Appeal Board Manual of Procedure, Registrant Anticancer, Inc. ("Registrant") hereby submits this Notice of Reliance during its testimony period. Anticancer is relying upon printouts from the website of the Center for Drug Evaluation and Research ("CDER"). The CDER is part of the Federal Drug Administration ("FDA").

The printouts from CDER's website are relevant because they support the conclusion that Registrant's mark ONCASE is not likely to cause confusion with Petitioner Alfacell Corp.'s ("Petitioner") mark ONCONASE because it is unlikely that both products will reach the market. Specifically, the printouts from CDER's website establish that the federal drug application process is a long and complex one. Both Registrant's ONCASE product and Petitioner's ONCONASE product are at very early stages in the application process.

The attached printouts from CDER's website meet all requirements for admissibility. Printed publications, including electronically generated documents, may be introduced in evidence by a notice of reliance. TBMP § 708; 37 C.F.R. § 2.122(e).

Based upon these authorities, Anticancer respectfully requests that the attached material be admitted in evidence.

Dated: April 11, 2003

Respectfully submitted,

By _____

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U.S. Food and Drug Administration • Center for Drug Evaluation and Research

# Drug Applications



## Drug Approval Application Process



## Introduction

The Center for Drug Evaluation and Research's (CDER) job is to ensure that drugs

are safe and effective. (See "*Benefit vs. Risk: How FDA Approves New Drugs*"). CDER does not test drugs, although the Center's Office of Testing and Research does conduct limited research in the areas of drug quality, safety, and effectiveness.

CDER is the largest of FDA's five centers, with a staff of about 1,800. It has responsibility for both prescription and over-the-counter drugs. For more information on CDER activities, including performance for drug reviews, post-marketing risk assessment, and other highlights, please see the *CDER 2001 Report to the Nation: Improving Public Health Through Human Drugs.* The other four FDA centers have responsibility for medical and radiological devices, food, and cosmetics, biologics, and veterinary drugs.

It is the responsibility of the company seeking to market a drug to test it and submit evidence that it is safe and effective. (See *"Testing Drugs in People"* in the July-August 1994 *FDA Consumer.*) A team of CDER physicians, statisticians, chemists, pharmacologists, and other scientists reviews the sponsor's new drug application (NDA) containing the data and proposed labeling.

For more information on drug development, drug review, and postmarketing activities please see these resources:

- *The FDA's Drug Review Process: Ensuring Drugs are Safe and Effective.* (7/2002). FDA Consumer magazine article.
- *From Test Tube to Patient: Improving Health Through Human Drugs* (9/99). In-depth review of drug development and postmarketing activities.
- New Drug Development in the United States. Online seminar provides healthcare professionals with an overview of FDA's role in the new drug development process.

The section below entitled *From Fish to Pharmacies: The Story of a Drug's Development*, illustrates how a drug sponsor can work with FDA's regulations and guidance information to bring a new drug to market.

## From Fish to Pharmacies:

## The Story of a Drug's Development

Osteoporosis, a crippling disease marked by a wasting away of bone mass, affects as many as 2 million American, 80 percent of them women, at an expense of $13.8 billion a year, according to the National Osteoporosis Foundation., The disease may be responsible for 5 million fractures of the hip, wrist and spine in people over 50, the foundation says, and may cause 50,000 deaths. Given the pervasiveness of osteoporosis and its cost to society, experts say it is crucial to have therapy alternatives if, for example, a patient can't tolerate estrogen, the first-line treatment.

Enter the salmon, which, like humans, produces a hormone called calcitonin that helps regulate calcium and decreases bone loss. For osteoporosis patients, taking salmon calcitonin, which is 30 times more potent than that secreted by the human thyroid gland, inhibits the activity of specialized bone cells called osteoclasts that absorb bone tissue. This enables bone to retain more bone mass.

Though the calcitonin in drugs is based chemically on salmon calcitonin, it is now made synthetically in the lab in a form that copies the molecular structure of the fish gland extract. Synthetic calcitonin offers a simpler, more economical way to create large quantities of the product.

FDA approved the first drug based on salmon calcitonin in an injectable. Since then, two more drugs, one injectable and one administered through a nasal spray were approved. An oral version of salmon calcitonin is in clinical trials now. Salmon calcitonin is approved only for postmenopausal women who cannot tolerate estrogen, or for whom estrogen is not an option.

*(Excerpted from FDA Consumer magazine, Jan-Feb 1999, "Drugs of the Deep: Treasures of the Sea Yield Some Medical Answers and Hint at Others," by John Henkel).*

How did the developers of injectable salmon calcitonin journey "from fish to pharmacies?"

For drug sponsors and others who want a basic understanding of the drug development process, the FDA has published a series of articles in a special report

called "*From Test Tube to Patient: Improving Health Through Human Drugs*" These articles provide background information on a broad range of topics from laboratory and animal studies, to reporting unsafe medical products already on the market. Another resource for drug development information is an interactive chart which graphically displays the process with an emphasis on preclinical (animal) research and clinical (human) studies or trials conducted by the drug's sponsor.

After obtaining promising data from laboratory studies, the salmon calcitonin drug developers took the next step and submitted an Investigational New Drug (IND) application to CDER. The IND Webpage explains the need for this application, the kind of information the application should include, and the Federal regulations to follow.

Once the IND application is in effect, the drug sponsor of salmon calcitonin could begin their clinical trials. After a sponsor submits an IND application, it must wait 30 days before starting a clinical trial to allow FDA time to review the prospective study. If FDA finds a problem, it can order a "clinical hold" to delay an investigation, or interrupt a clinical trial if problems occur during the study.

Clinical trials are experiments that use human subjects to see whether a drug is effective, and what side effects it may cause. The Information for Clinical Investigators Webpage provides links to the regulations and guidelines that the clinical investigators of salmon calcitonin must have used to conduct a successful study, and to protect their human subjects.

The salmon calcitonin drug sponsor analyzed the clinical trials data and concluded that enough evidence existed on the drug's safety and effectiveness to meet FDA's requirements for marketing approval. The sponsor submitted a New Drug Application (NDA) with full information on manufacturing specifications, stability and bioavailablility data, method of analysis of each of the dosage forms the sponsor intends to market, packaging and labeling for both physician and consumer, and the results of any additional toxicological studies not already submitted in the Investigational New Drug application. The NDA Webpage provides resources and guidance on preparing the NDA application, and what to expect during the review process.

New drugs, like other new products, are frequently under patent protection during development. The patent protects the salmon calcitonin sponsor's investment in the drug's development by giving them the sole right to sell the drug while the patent is in effect. When the patents or other periods of exclusivity on brand-name drugs expire, manufacturers can apply to the FDA to sell generic versions. The Abbreviated New Drug Applications (ANDA) for Generic Drug Products Webpage provides links to guidances, laws, regulations, policies and procedures, plus other resources to assist in preparing and submitting applications.

Drug sponsors from small businesses can take advantage of special offices and programs designed to help meet their unique needs. The Small Business Assistance Webpage provides links to FDA laws, regulations and guidances that affect small business. Information is also provided on financial assistance and incentives that are available for drug development.

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**FDA/Center for Drug Evaluation and Research**
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**HTML by SJW**

U.S. Food and Drug Administration • Center for Drug Evaluation and Research

# Drug Applications



## Laws, Regulations, Policies and Procedures for Drug Applications

- Investigational New Drug Applications and New Drug Applications
  - *Code of Federal Regulations*
  - Manual of Policies and Procedures (MaPPs) UPDATED
- Abbreviated New Drug Applications for Generic Drug Products
  - *Code of Federal Regulations*
  - Manual of Policies and Procedures (MaPPs)

The mission of FDA is to enforce laws enacted by the U.S. Congress and regulations established by the Agency to protect the consumer's health, safety, and pocketbook. *The Federal Food, Drug, and Cosmetic Act* is the basic food and drug law of the U.S. With numerous amendments it is the most extensive law of its kind in the world. The law is intended to assure the consumer that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging is truthful, informative, and not deceptive.

## Investigational New Drug Applications and New Drug Applications

The following *Code of Federal Regulations* sections provide regulations for INDs and NDAs. All parts of section 21 of the *Code of Federal Regulations* are also available.

| | |
|---|---|
| 21*CFR* Part 312 | Investigational New Drug Application |
| 21*CFR* Part 310 | New Drugs |
| 21*CFR* Part 314 | INDA and NDA (New Drug Approval) |

| | |
|---|---|
| 21*CFR* Part 320 | Bioavailability and Bioequivalence Requirements |
| 21*CFR* Part 316 | Orphan Drugs |
| 21*CFR* Part 58 | Good Lab Practice for Animal Studies |
| 21*CFR* Part 201.23 | Required Pediatric Studies |
| 21*CFR* Part 50 | Protection of Human Subjects |
| 21*CFR* Part 56 | Institutional Review Boards |
| 21*CFR* Part 201 | Drug Labeling |
| 21*CFR* Part 54 | Financial Disclosure by Clinical Investigators |

**MaPPs.** The following MaPPs provide official instructions for internal practices and procedures followed by CDER staff to help standardize the IND and NDA review process. All CDER MaPPs are available from the MaPP Index webpage.

- 5240.4 Submission of an IND Application to the Office of Generic Drugs
- 6030.1 IND Process and Review Procedures (Including Clinical Holds)
- 6030.4 INDs: Screening INDs. (Issued 5/9/2001, Posted 5/14/2001) New!!
- 6050.1 Refusal to Accept Application for Filing From Applicants in Arrears
- 7211.1 Drug Application Approval 501(b) Policy

## Abbreviated New Drug Application (ANDA) for Generic Drug Products

The following *Code of Federal Regulations* sections provide regulations for ANDAs. All parts of section 21 of the *Code of Federal Regulations* are also available.

| | |
|---|---|
| 21*CFR* Part 314 | Applications for FDA Approval to Market a New Drug or an Antibiotic Drug |
| 21*CFR* Part 320 | Bioavailability and Bioequivalence Requirements |
| 21*CFR* Part 310 | New Drugs |

**MaPPs** The following MaPPs provide official instructions for internal practices and procedures followed by CDER staff to help standardize the ANDA review process. All CDER MaPPs are available from the MaPP Index webpage

Chapter 5200 - Generic Drugs

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# Drug Applications

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## Frequently Asked Questions on Drug Development and Investigational New Drug Applications

Investigational New Drug Process

- An Introduction
- Definitions
- Types of INDs
- Phases of an Investigation

Investigational New Drug Application

- What are the FDA requirements for pre-clinical studies?
- What is an Investigational New Drug Application?
- Do I need to submit an Investigational New Drug Application?
- Where do I get the necessary updated forms?
- Are there instructions to help you fill out the forms?
- When will I be assigned an IND number?
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- Do I need to fill out a Statement of Investigator Form 1572?
- What is an Institutional Review Board?
- Does a physician, in private practice, conducting research with an FDA regulated product, need to obtain IRB approval?
- Does a clinical investigation involving a marketed product require IRB review and approval?
- Do I need informed consent?
- What are the specific divisions and contacts in CDER who can answer my questions?

## INVESTIONATIONAL NEW DRUG PROCESS

An Introduction

This website is designed for individuals interested in bringing a drug to market. This may be an individual or pharmaceutical company, governmental agency, academic institution, or other type of organization.

The main purpose of an Investigational New Drug (IND) application is to provide the data showing that it is reasonable to begin tests of a new drug on humans. Also, current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

The IND is not an application for marketing approval.

Definitions

- Clinical investigation means any experiment in which a drug is administered or dispensed to one or more human subjects.
- Investigator means an individual under whose immediate direction the drug is administered or dispensed to a subject.
- Sponsor means a person who takes responsibility for and initiates a clinical investigation.

- Sponsor-Investigator means an individual who both initiates and conducts an investigation and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual.

- For more definitions, see Drug Development and Review Definitions.

Types of INDs

"Commercial INDs" are applications that are submitted primarily by companies whose ultimate goal is to obtain marketing approval for a new product.

- Noncommercial INDs, filed for noncommercial research
- Investigator INDs
- Emergency Use INDs

Emergency and Treatment INDs are also known as "Compassionate" INDs, but the term "Compassionate" is not in the IND regulations.

A sponsor shall submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug A sponsor shall not begin a clinical trial until the investigation is subject to an approved IND application. A sponsor shall submit a separate IND for any clinical investigation involving an exception from informed consent.

Phases of an Investigation

An IND may be submitted for one or more phases of an investigation. The clinical investigation of a previously untested drug is generally divided into three phases. Although in general the phases are conducted sequentially, they may overlap. The three phases of an investigation are as follows:

Phase 1 includes the initial introduction of an investigational new drug into humans. These studies are usually conducted in healthy volunteer subjects. These studies are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects

associated with increasing doses, and, if possible, to gain early evidence on effectiveness. Phase 1 studies also evaluate drug metabolism, structure-activity relationships, and the mechanism of action in humans. The total number of subjects included in Phase 1 studies is generally in the range of twenty to eighty.

Phase 2 includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition. This phase of testing also helps determine the common short-term side effects and risks associated with the drug. Phase 2 studies usually involve several hundred people.

Phase 3 studies are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug. Phase 3 studies also provide an adequate basis for extrapolating the results to the general population and transmitting that information in the physician labeling. Phase 3 studies usually include several hundred to several thousand people.

## INVESTIGATIONAL NEW DRUG APPLICATION

### What are the FDA requirements for pre-clinical studies?

Under FDA requirements, a sponsor must first submit data showing that the drug is reasonably safe for use in initial, small-scale clinical studies. Depending on whether the compound has been studied or marketed previously, the sponsor may have several options for fulfilling this requirement: (1) compiling existing nonclinical data from past *in vitro* laboratory or animal studies on the compound; (2) compiling data from previous clinical testing or marketing of the drug in the United States or another country whose population is relevant to the U.S. population; or (3) undertaking new preclinical studies designed to provide the evidence necessary to support the safety of administering the compound to humans.

During preclinical drug development, a sponsor evaluates the drug's toxic and pharmacologic effects through *in vitro* and *in vivo* laboratory animal testing.

Genotoxicity screening is performed, as well as investigations on drug absorption and metabolism, the toxicity of the drug's metabolites, and the speed with which the drug and its metabolites are excreted from the body. At the preclinical stage, the FDA will generally ask, at a minimum, that sponsors: (1) develop a pharmacological profile of the drug; (2) determine the acute toxicity of the drug in at least two species of animals, and (3) conduct short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical studies.

**What is an Investigational New Drug Application?**

In many ways, the investigational new drug (IND) application is the result of a successful preclinical development program. The IND is also the vehicle through which a sponsor advances to the next stage of drug development known as clinical trials (human trials).

**Do I need to submit an IND?**

"Investigational use" suggests the use of an approved product in the context of a clinical study protocol. When the principal intent of the investigational use of a test article is to develop information about the product's safety or efficacy, submission of an IND may be required. However, the clinical investigation of a marketed drug or biologic does not require submission of an IND if all six of the following conditions are met:

(1) it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;

(2) it is not intended to support a significant change in the advertising for the product;

(3) it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the

drug product;

(4) it is conducted in compliance with the requirements for IRB review and informed consent [21 *CFR* parts 56 and 50, respectively];

(5) it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 *CFR* 312.7]; and

(6) it does not intend to invoke 21 *CFR* 50.24.

**Where do I get the necessary updated forms?**

The forms needed are 1571 and 1572.

**Are there instructions to help you fill out the forms?**

Instructions for completing FDA forms 1571 and 1572

**When will I be assigned an IND number?**

An IND number will be assigned after the IND application is received by FDA..

**When can I start clinical trials?**

Unless you are contacted, you may begin trials thirty days after FDA receives your IND application.

**Do I need to fill out a Statement of Investigator Form 1572?**

Yes. Investigators may participate in an investigation only after they provide the sponsor with a completed, signed Statement of Investigator Form FDA 1572.

**What is an Institutional Review Board?**

Under FDA regulations, an Institutional Review Board (IRB) is a group that has been formally designated to review and monitor biomedical research involving human subjects. In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research.

Institutional Review Boards are used to ensure the rights and welfare of people participating in clinical trials both before and during their trial participation. IRBs use a group process to review research protocols and related materials (e.g., informed consent documents and investigator brochures) to ensure protection of the rights and welfare of human subjects of research. IRBs at hospitals and research institutions throughout the country make sure that participants are fully informed and have given their written consent before studies ever begin. IRBs are monitored by the FDA to protect and ensure the safety of participants in medical research.

An IRB must be composed of no less than five experts and lay people with varying backgrounds to ensure a complete and adequate review of activities commonly conducted by research institutions. In addition to possessing the professional competence needed to review specific activities, an IRB must be able to ascertain the acceptability of applications and proposals in terms of institutional commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes. Therefore, IRBs must be composed of people whose concerns are in relevant areas.

**Does a physician, in private practice, conducting research with an FDA regulated product, need to obtain IRB approval?**

Yes. The FDA regulations require IRB review and approval of regulated clinical investigations, whether or not the study involves institutionalized subjects. FDA has included non-institutionalized subjects because it is inappropriate to apply a double standard for the protection of research subjects based on whether or not they are institutionalized. An investigator may be able to obtain IRB review by submitting the research proposal to a community hospital, a university/medical school, an

independent IRB, a local or state government health agency or other organizations. If IRB review cannot be accomplished by one of these means, investigators may contact the FDA for assistance (Health Assessment Policy Staff 301-827-1685).

**Does a clinical investigation involving a marketed product require IRB review and approval?**

Yes, if the investigation is governed by FDA regulations [see 21 *CFR* 56.101, 56.102(c), 312.2(b)(1), 361.1, 601.2, and 812.2].

**Do I need informed consent?**

Yes. Investigators may involve a human being as a subject in research only after they have obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

**What are the specific divisions and contacts in CDER who can answer my questions?**

The Food and Drug Administration's Center for Drug Evaluation and Research is dedicated to ensuring that all persons involved in, or who depend upon, drug regulation have the information needed to develop, review, market, dispense, prescribe or use drugs safely and effectively.

Any of these individuals or groups may request information on specific drugs, guidance documents, publications, or general information such as

a description of the drug approval process.

There are a number of ways consumers and industry representatives can communicate with or get reliable, current, and up-to-date information from the Center.

- The newest, and easiest, method for getting information is the Center's Web Page at http://www.fda.gov/cder.
- For more specific or complex drug inquiries, telephone the Drug Information Branch at (301) 827-4573 or send them an electronic mail message at druginfo@cder.fda.gov.

Other sources of information include:

- FDA Office of Consumer Affairs at 1-800-532-4440, or locally at (301) 827-4420; and
- FDA Office of Public Affairs, at 301-827-6250.
- Organization, Contact, and Meeting Information

In addition, consumers and industry representatives can contact:

- CDER Ombudsman, Jim Morrison, (301) 594-5443;
- FDA Freedom of Information Staff, (301) 827-6567;
- FDA MedWatch Office at 1-800-FDA-1088;
- AIDS Clinical Trials Information Service, 1-800-TRIALS-A or on the World Wide Web at http://www.actis.org

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# Drug Applications

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## Investigational New Drug (IND) Application Process



## Introduction

Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means

through which the sponsor technically obtains this exemption from the FDA.

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer) having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans. At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system.

There are three types of INDs:

- An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.
- Emergency Use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR , Sec. 312.23 or Sec. 312.34. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
- Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

The IND application must contain information in three broad areas:

- Animal Pharmacology and Toxicology Studies - Preclinical data to permit an

assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experience with the drug in humans (often foreign use).

- Manufacturing Information - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.

- Clinical Protocols and Investigator Information - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators--professionals (generally physicians) who oversee the administration of the experimental compound--to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk.

This interactive chart summarizes the IND process, including how CDER determines if the product is suitable for use in clinical trials.

*This web site is designed for individuals from pharmaceutical companies, government agencies, academic institutions, private organizations, or other organizations interested in bringing a new drug to market. Each of the sections below contains information from CDER to assist you in the IND application process. For specific information, click on a link to go directly to a section or webpage.*

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## Resources for IND Applications

The following resources have been gathered to provide you with the legal requirements of an IND application, assistance from CDER to help you meet those requirements, and internal IND review principles, policies and procedures.

**Office of Drug Evaluation (ODE) IV: Pre-IND Consultation Program** (Updated 8/31/99). The ODE IV Pre-Investigational New Drug Application (IND) Consultation Program is designed to facilitate and foster informal early communications between the divisions of ODE IV and potential sponsors of new therapeutics for the treatment of bacterial infections, HIV, opportunistic infections, transplant rejection, and other diseases. The program is intended to serve sponsors of all drug products that may be submitted to any division within ODE IV, including but not limited to drugs for the treatment of life-threatening illnesses.

## Guidance Documents for INDs

Guidance documents represent the Agency's current thinking on a particular subject. These documents are prepared for FDA review staff and applicants/sponsors to provide guidelines to the processing, content, and evaluation/approval of applications and also to the design, production, manufacturing, and testing of regulated products. They also establish policies intended to achieve consistency in the Agency's regulatory approach and establish inspection and enforcement procedures. Because guidances are not regulations or laws, they are not enforceable, either through administrative actions or through the courts. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. For information on a specific guidance document, please contact the originating office.

For the complete list of CDER guidances, please see the Guidance Index. Most of these documents are in Adobe Acrobat format, also know as PDF. The free upgrade to Adobe Acrobat 3.0 or higher is recommended, especially if you have difficulty opening any of the documents below. Another method of obtaining guidance documents is through the Drug Information Branch, Division of Communications and Management.

Guidance documents to help prepare INDs include:

- Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs Including Well Characterized, Therapeutic, Biotechnology-Derived Products. Provides description of required sections of an application.
- Q & A - Content and Format of INDs for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products. Optional Format: PDF. This guidance is intended to clarify when sponsors should submit final, quality-assured toxicology reports and/or update the Agency on any changes in findings since submission of non-quality-assured reports or reports based on non-quality-assured data. (Issued 10/00).
- Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations. Optional Format: PDF (Issued 10/2000, Posted 10/27/2000). This guidance should be useful for applicants planning to conduct bioavailability (BA) and bioequivalence (BE) studies during the IND period for an NDA, BE studies intended for submission in an ANDA, and BE studies conducted in the postapproval period for certain changes in both NDAs and ANDAs.
- Drug Master Files. A Drug Master File (DMF) is a submission to the Food and Drug Administration (FDA) that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.
- Required Specifications for FDA's IND, NDA, and ANDA Drug Master File Binders.
- Immunotoxicology Evaluation of Investigational New Drugs [Word] or [PDF] (Issued 10/2002, Posted 10/31/2002). This guidance makes recommendations to sponsors of investigational new drugs (INDs) on (1) the parameters that should be routinely assessed in toxicology studies to determine effects of a drug on immune function, (2) when additional immunotoxicity studies should be conducted, and (3) when additional mechanistic information could help characterize the significance of a given drug's effect on the immune system.

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## Laws, Regulations, Policies and Procedures

The mission of FDA is to enforce laws enacted by the U.S. Congress and regulations established by the Agency to protect the consumer's health, safety, and pocketbook. *The Federal Food, Drug, and Cosmetic Act* is the basic food and drug law of the U.S. With numerous amendments it is the most extensive law of its kind in the world. The law is intended to assure consumers that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging is truthful, informative, and not deceptive.

### *Code of Federal Regulations* (CFR)

*Code Of Federal Regulations* (CFR). The final regulations published in the *Federal Register* (daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the *CFR*. The *CFR* is divided into 50 titles that represent broad areas subject to Federal regulations. The FDA's portion of the *CFR* interprets the *Federal Food, Drug and Cosmetic Act* and related statutes. Section 21 of the *CFR* contains most regulations pertaining to food and drugs. The regulations document all actions of all drug sponsors that are required under Federal law.

- The following regulations apply to the IND application process:

| | |
|---|---|
| 21CFR Part 312 | Investigational New Drug Application |
| 21CFR Part 314 | INDA and NDA (New Drug Approval) |
| 21CFR Part 316 | Orphan Drugs |
| 21CFR Part 58 | Good Lab Practice for Animal Studies |
| 21CFR Part 50 | Protection of Human Subjects |
| 21CFR Part 56 | Institutional Review Boards |
| 21CFR Part 201 | Drug Labeling |
| 21CFR Part 54 | Financial Disclosure by Clinical Investigators |

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### MaPPs

CDER's Manual of Policies and Procedures (MaPPs). These documents are approved instructions for internal practices and procedures followed by CDER staff to help standardize the new drug review process and other activities. MaPPs define external activities as well. All MAPPs are available for the public to review to get a better understanding of office policies, definitions, staff responsibilities and procedures. MaPPs of particular interest to IND sponsors include:

- 5240.4 Submission of an IND Application to the Office of Generic Drugs (OGD). OGD policy and procedures regarding submissions on INDs for bioequivalence studies. These INDs are called Bio-INDs to distinguish them from clinical INDs submitted to CDER's new drug reviewing divisions.
- 6030.1 IND Process and Review Procedures (Including Clinical Holds). Includes general IND review principles, policies and procedures for issuing clinical holds of INDs, and processing and responding to sponsors' complete responses to clinical holds.
- 6030.4 INDs: Screening INDs. (Issued 5/9/2001, Posted 5/14/2001). This MsPP describes procedures for the review of multiple active moieties or formulations under the single investigative new drug application (IND) called a screening IND.

## IND Forms and Instructions

Forms for use in submitting INDs include:

- FDA 1571 Investigational New Drug Application
- FDA 1572 Statement of Investigator
- Instructions for completing FDA forms 1571 and 1572
- FDA Form Distributions Page includes links to:
  Certification: Financial Interest and Arrangements of Clinical Investigators
  Disclosure: Financial Interest and Arrangements of Clinical Investigators
  MedWatch: FDA Medical Product Reporting Program - Voluntary

MedWatch: FDA Medical Products Reporting Program - Mandatory
- For electronic form submissions, see ERSR

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## Emergency use of an Investigational Drug or Biologic

- The Guidance for Institutional Review Boards and Clinical Investigators contains information on: Obtaining an Emergency IND, Emergency Exemption from Prospective IRB, Approval Exception from Informed Consent, and Requirement Planned Emergency Research, Informed Consent Exception.

- For assistance in obtaining unapproved cancer drugs, please see Access to Unapproved Drugs.

## Targeted Product Information (TPI) Project

After a 12-month collaborative effort between FDA and the Pharmaceutical Research Manufacturers Association (PhRMA), FDA's Office of Drug Evaluation IV (ODE IV) started a pilot test of a tool that may improve the drug development process. This tool is the Targeted Product Information (TPI) Document. The sponsor writes the TPI to guide the design, conduct, and analysis of clinical trials so that at the end of the development program, the sponsor will have gathered the necessary data to support the sponsor's desired outcome -- the approval and appropriate labeling, or package insert, of the drug under development.

- TPI Program Overview. Includes background information, intent of the TPI document, what the TPI document is and is not, plus a summary.
- TPI Template. The template provides a recommended outline for a TPI with a description of suggested information for each section.

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## Related Topics

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**FDA/Center for Drug Evaluation and Research**
**Last Updated: November 7, 2002**
**Originator: OTCOM/DML**
**HTML by SJW**

U.S. Food and Drug Administration • Center for Drug Evaluation and Research

# Drug Applications

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APPLICATION PROCESS:
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## New Drug Application (NDA) Process



## Introduction

For decades, the regulation and control of new drugs in the United States has been based on the New Drug Application (NDA). Since 1938, every new drug has been the subject of an approved NDA before U.S. commercialization. The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S. The data gathered during the animal studies and human clinical trials of an Investigational New Drug (IND) become part of the NDA.

The goals of the NDA are to provide enough information to permit FDA reviewer to reach the following key decisions:

- Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.
- Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain.
- Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

The documentation required in an NDA is supposed to tell the drug's whole story, including what happened during the clinical tests, what the ingredients of the drug are, the results of the animal studies, how the drug behaves in the body, and how it is manufactured, processed and packaged. The following resources provide summaries on NDA content, format, and classification, plus the NDA review process:

- For a brief history of U.S. drug law, please see Benefit vs. Risk: How CDER Approves New Drugs.
- The New Drug Development section of the CDER Handbook provides an understanding of how CDER works to assure that safe and effective drugs are available to the American people.
- New Drug Application (NDA) Review Process Chart provides a general overview of CDER's new drug application review process, including how CDER determines the benefit:risk profile of a drug product prior to approval for marketing.
- Review Diagram Project provides links to several flowcharts from CDER review divisions that show the framework, content, process and issues involved in review activity. The diagrams represent attempts by individual medical officers to visualize their own review processes; they do not represent official CDER or division standards.

*This web site is designed for individuals from pharmaceutical companies, government agencies, academic institutions, private organizations, or their organizations interested in bringing new drugs to market. Each of the sections below contains information from CDER to assist you in the NDA application process. For*

*specific information, click on a link to go directly to a section or webpage.*

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## Resources for NDA Submissions

The following resources have been gathered to provide you with the legal requirements of a new drug application, assistance from CDER to help you meet those requirements, and internal NDA review principles, policies and procedures.

### Guidance Documents for NDAs

Guidance documents represent the Agency's current thinking on a particular subject. These documents are prepared for FDA review staff and applicants/sponsors to provide guidelines to the processing, content, and evaluation/approval of applications and also to the design, production, manufacturing, and testing of regulated products. They also establish policies intended to achieve consistency in the Agency's regulatory approach and establish inspection and enforcement procedures. Because guidances are not regulations or laws, they are not enforceable, either through administrative actions or through the courts. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. For information on a specific guidance document, please contact the originating office.

For the complete list of CDER guidances, please see the Guidance Index. Most of these documents are in Adobe Acrobat format, also know as PDF. The free upgrade to Adobe Acrobat 3.0 or higher is recommended, especially if you have difficulty opening any of the documents below. Another method of obtaining guidance documents is through the Drug Information Branch, Division of Communications and Management.

Guidance documents to help prepare NDAs include:

- Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations. Optional Format: PDF (Issued 10/2000, Posted 10/27/2000). This guidance should be useful for applicants planning to conduct bioavailability (BA) and bioequivalence (BE) studies during the IND period for an NDA, BE studies intended for submission in an ANDA, and BE studies conducted in the postapproval period for certain changes in both NDAs and ANDAs.
- Container Closure Systems for Packaging Human Drugs and Biologics. (Issued 5/1999, Posted 7/6/1999)
- Format and Content of the Chemistry, Manufacturing and Controls Section of an Application. (Issued 2/1987, Posted 3/2/1998)
- Format and Content of the Microbiology Section of an Application.
- Format and Content of the Clinical and Statistical Sections of an Application. (Issued 7/1988, Posted 5/21/1997)
- Format and Content of the Summary for New Drug and Antibiotic Applications. (Issued 2/1987, Posted 3/2/1998)
- Formatting, Assembling and Submitting New Drug and Antibiotic Applications. (Issued 2/1987, Posted 3/2/1998)
- Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances.
- Submitting Documentation for the Stability of Human Drugs and Biologics. (Issued 2/1987, Posted 3/2/1998)
- Submitting Samples and Analytical Data for Methods Validation.
- Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Products.
- Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application. (Issued 2/1987, Posted 3/2/1998)
- Format and Content of the Nonclinical Pharmacology/Toxicology Section of an Application. (Posted 3/2/1998)
- Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. Describes the quantity of evidence, and the documentation of the quality of evidence necessary to support a claim of drug effectiveness.
- Drug Master Files. A Drug Master File (DMF) is a submission to the FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.

- Required Specifications for FDA's IND, NDA, and ANDA Drug Master File Binders
- Qualifying for Pediatric Exclusivity. Certain applications may be able to obtain an additional six months of patent exclusivity.
- Refusal to File. (Issued 7/12/1993, Posted 11/26/99) Clarifies CDER's decisions to refuse to file an incomplete application.

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## Laws, Regulations, Policies and Procedures

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- 21CFR Part 314 - Applications for FDA Approval to Market a New Drug or an Antibiotic Drug.

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- 6050.1. Refusal to Accept Application for Filing From Applicants in Arrears
- 7211.1. Drug Application Approval 501(b) Policy
- 7600.6. Requesting and Accepting Non-Archivable Electronic Records for New Drug Applications.

## Prescription Drug User Fee Act (PDUFA)

On November 21, 1997, The President signed the Food and Drug Administration Modernization Act of 1997. This legislation includes authorization for FDA to continue to collect three types of user fees from applicants who submit certain new drug and biological product applications. FDA was first authorized to collect user fees under the Prescription Drug User Fee Act (PDUFA) of 1992.

- Prescription Drug User Fee Act Related Documents

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## NDA Forms and Electronic Submissions

- Form FDA-356h. Application to Market a New Drug, Biologic, or An Antibiotic Drug For Human Use
- Form FDA-3397. User Fee Cover Sheet
- Form FDA-3331. New Drug Application Field Report
- Guidance Documents for Electronic Submissions
- For more information on electronic submissions, see ERSR

## Advisory Committees

Advisory committees provide independent advice and recommendations to the FDA on scientific and technical matters related to the development and evaluation of products regulated by the Agency. CDER requests advice from advisory committees on a variety of matters, including various aspects of clinical investigations and applications for marketing approval of drug products. Committee members are scientific experts such as physician-researchers and statisticians, as well as representatives of the public, including patients. Although the committees provide recommendations to the Agency, final decisions are made by FDA.

- CFR 21 Part 14 Public Hearing Before a Public Advisory Committee. Detailed description of advisory committees from the *Code of Federal Regulations*.
- Guidance for Industry: Advisory Committees. Includes information on membership, conflict of interest, scheduling, and action on recommendations.
- List of Tentative Meeting Dates for Advisors and Consultants Staff. Several dates have been set aside by CDER advisory committees for possible future meetings. The subject matter and location of the meetings (if they are held) will be published in the *Federal Register* in the month prior to the meeting date.
- FDA Meeting Transcripts 1995 to Present. Recent transcripts includes minutes, briefing information, slides and other documents.

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## Targeted Product Information (TPI) Project

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## Related Topics

- Investigational New Drug Application (IND) Webpage Provides resources to assist drug sponsors with submitting applications for approval to begin new drug experiments on human subjects.
- Abbreviated New Drug Application (ANDA) Webpage Provides resources to assist drug sponsors with submitting applications to market a generic drug.
- Combination Products Program Combination products often involve cutting edge, novel technologies that raise not only unique scientific and technical questions, but also regulatory challenges related to where and how they should be regulated in order to ensure adequate and consistent regulatory oversight. New!! (Posted 9/5/2002)
- Drug Application Regulatory Compliance The approval process for new drug applications includes a review of the manufacturer's compliance with Current Good Manufacturing Practice. This web page provides resources to help meet compliance.
- Post Drug-Approval Activities The goal of CDER's post drug-approval activities is to monitor the ongoing safety of marketed drugs. This is accomplished by reassessing drug risks based on new data learned after the drug is marketed, and recommending ways of trying to most appropriately manage that risk.
- Information for Clinical Investigators Webpage Provides regulations and guidelines to scientists who design and run experiments (clinical trials) to test the safety and effectiveness of new drugs on human subjects.
- Small Business Assistance Program Webpage.
- Electronic Regulatory Submission and Review (ERSR) Webpage Provides information on electronic drug applications, application reviews, Electronic Document Room, and other ERSR projects.

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**FDA/Center for Drug Evaluation and Research**
**Last Updated: September 5, 2002**
**Originator: OTCOM/DML**
**HTML by PKS, SJW**

## PROOF OF SERVICE BY OVERNIGHT DELIVERY

I declare that I am employed with the law firm of Morrison & Foerster LLP, whose address is 425 Market Street, San Francisco, California, 94105; I am not a party to the within cause; I am over the age of eighteen years and I am readily familiar with Morrison & Foerster's practice for collection and processing of correspondence for overseas delivery and know that in the ordinary course of Morrison & Foerster's business practice the document described below will be deposited in a box or other facility regularly maintained by UPS or delivered to an authorized courier or driver authorized by UPS to receive documents on the same date that it is placed at Morrison & Foerster for collection.

I further declare that on the date hereof I served a copy of:

**Registrant Anticancer, Inc.'s Notice of Reliance: Printouts from Website of The Center for Drug Evaluation and Research**

on the following by placing a true copy thereof enclosed in a sealed envelope with delivery fees provided for, addressed as follows for collection by UPS at Morrison & Foerster LLP, 425 Market Street, San Francisco, California, 94105, in accordance with Morrison & Foerster's ordinary business practices:

Mark H. Jay, Esq.
Mark H. Jay, P.A.
71 Baltusrol Way
Short Hills, NJ 07078-2457

I declare under penalty of perjury under the laws of the State of California that the above is true and correct.

Executed at San Francisco, California, this 11th day of April, 2003.

Lucia M. Sario

(signature)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | |
|---|---|
| Petitioner: | Alfacell Corporation |
| Registrant: | Anticancer, Inc. |
| Mark: | ONCASE |
| Reg. No.: | 1,987,445 |
| Cancellation No.: | 32,202 |

**CERTIFICATE OF MAILING BY EXPRESS MAIL**

Trademark Trial and Appeal Board
Assistant Commissioner for Trademarks
2900 Crystal Drive
Arlington, VA 22202-3513

Dear Sir:

Express Mail Label No.: EV 240722497 US

Date of Deposit: April 11, 2003

I hereby certify that the attached **Registrant Anticancer, Inc.'s Notice of Reliance: Website of Opposer Alfacell Corp.,; Registrant Anticancer, Inc.'s Notice of Reliance: Printouts from Website of The Center for Drug Evaluation and Research; Registrant Anticancer, Inc.'s Notice of Reliance: Printouts from Website of The Office of Drug Safety; Registrant Anticancer, Inc.'s Notice of Reliance: Article from The Journal Pharmaceutical Executive; Websites Showing The Circulation of Various Scientific Journals** and receipt verification postcard are being deposited with the United States Postal Service Express Mail delivery as "Express Mail Post Office to Addressee" service under 37 C.F.R § 1.10 on the date indicated above, and is addressed to: Trademark Trial and Appeal Board, Assistant Commissioner for Trademarks, 2900 Crystal Drive, Arlington, VA 22202-3513.

Respectfully submitted,

By: _____
Chase Trombella

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE TRADEMARK TRIAL AND APPEAL BOARD

| | |
|---|---|
| Alfacell Corporation<br>Petitioner | Cancellation No.: 32,202<br>Registration No. 1,987,445 |
| vs. | |
| Anticancer, Inc.<br>Registrant | |



**REGISTRANT ANTICANCER, INC.'S NOTICE OF RELIANCE: WEBSITES SHOWING THE CIRCULATION OF VARIOUS SCIENTIFIC JOURNALS**

Pursuant to 37 C.F.R. § 2.122(d)(2) and Rule 703.02(a) of the Trademark Trial and Appeal Board Manual of Procedure, Registrant Anticancer, Inc. ("Registrant") hereby submits this Notice of Reliance during its testimony period. Anticancer is relying upon the following: a printout from the website of the American Association for Cancer Research, showing circulation information for the journals *Cancer Research* and *Clinical Cancer Research*; a printout from the website of *The Journal of the National Cancer Institute* showing that journal's circulation information; a printout from the International Institute of Anticancer Research showing circulation information for the journal *Anticancer Research*; a printout from the website of the National Academies, showing circulation information for *Proceedings of the National Academy of Sciences of the United States of America*; and printouts from the *Gale Database of Publications and Broadcast Media* showing circulation information for the journals *Proceedings of the National Academy of Sciences of the United States of America*, *Clinical Cancer Research*, and *Cancer Research*.

These printouts are relevant because they support the conclusion that Registrant's mark ONCASE is not likely to cause confusion with Petitioner Alfacell Corp.'s ("Petitioner") mark ONCONASE given that there has yet been no actual confusion despite a long period of concurrent

use in overlapping channels of trade. Specifically, the printouts establish that the journals in which the ONCASE product and the ONCONASE product were discussed are journals of wide distribution. The Board recognizes that under the *Du Pont* likelihood of confusion analysis, a long period of concurrent, simultaneous use of two marks, without any instances of actual confusion is persuasive evidence that there is no likelihood of confusion between the two marks. *Application of E.I. DuPont DeNemours & Co.*, 476 F.2d 1357, 1361, 177 U.S.P.Q. (BNA) 563, 567 (C.C.P.A. 1973); *G.H. Mumm & Cie v. Desnoes & Geddes Ltd.*, 917 F.2d 1292, 16 USPQ2d 1635, 1638 (Fed. Cir. 1990); *Marcal Paper Mills, Inc. v. American Can Company*, 1981 TTAB LEXIS 9 at *39.

The attached printouts meet all requirements for admissibility. Printed publications, including electronically generated documents, may be introduced in evidence by a notice of reliance. TBMP § 708; 37 C.F.R. § 2.122(e).

Based upon these authorities, Anticancer respectfully requests that the attached material be admitted in evidence.

Dated: April 11, 2003

Respectfully submitted,

By _____

Jennifer Lee Taylor
Attorney for Registrant

MORRISON & FOERSTER LLP
425 Market Street
San Francisco, California 94105-2482
Telephone: (415) 268-6538
Facsimile: (415) 268-7522

American Association for Cancer Research 93rd Annual Meeting



AACR Annual Meeting Home

Opportunities for Corporate Participation

Sponsorship

Exhibiting

Advertising

Advance Registration Mail List

## Advertising

Expand your company's presence at the AACR annual meeting by placing an ad in one or more of the AACR publications listed below. Combined frequency rates are available for ads placed in the Program and any AACR journal. Each of these publications will be distributed to meeting attendees, giving your promotional message high visibility among an influential group of cancer professionals.

**AACR 92nd Annual Meeting Program**
An important resource that is distributed to all meeting attendees, as well as AACR members who subscribe to any AACR journal. Circulation: 19,000.

**Cancer Research**
The most-cited cancer journal in the world. A vital source of groundbreaking research for cancer professionals worldwide. Circulation: 9,500.

**Clinical Cancer Research**
A valuable publication for oncologists and other cancer professionals who require reports of the latest clinical and translational cancer studies. Circulation: 4,600.

**Cancer Epidemiology, Biomarkers & Prevention**
A highly ranked journal that provides international coverage of three dynamic fields. Circulation: 2,800.

**Cell Growth & Differentiation**
A timely source of research into normal and abnormal cell behavior and cell growth control. Circulation: 2,400.

**Molecular Cancer Therapeutics**
A new AACR journal launching in Fall 2001. Featuring basic research studies that have an impact on cancer therapeutics. Consider advertising in the March 2002 issue, which will be distributed at the 93rd AACR Annual Meeting.

To reserve your ad space, or for more information:
Contact M. J. Mrvica Associates, Inc.
Telephone: (856) 768-9360
FAX: (856) 753-0064

# Advertising Rates
## *Journal of the National Cancer Institute*

**For Advertising Insertion Orders**

PRC Associates, The Annexe, Fitznells Manor, Chessington Road, Ewell, Surrey, KT17 1TF, UK.
Tel: +44 (0) 020 8786 7376
Fax: +44 (0) 020 8786 7262
Email: mail@prcassoc.co.uk

**Journal Contact** (express mail address)

Advertising Coordinator
Journal of the National Cancer Institute
Suite 500, 8120 Woodmont Ave.
Bethesda, MD 20814-2743
USA

Tel: 301-841-1284
Fax: 301-841-1299
E-mail: halbirtk@oupjournals.org

**WHY THE WORLD'S LEADING CANCER SPECIALISTS AND THE INTERNATIONAL BIOMEDICAL COMMUNITY TURN FIRST TO THE *JOURNAL OF THE NATIONAL CANCER INSTITUTE*:**

- **AUTHORITATIVE**

  The most respected and trusted in the cancer field.

- **INFLUENTIAL**

  The world's most cited original-research cancer journal, a position it has held since 1994.

- **ACCESSIBLE**

  Journal staff edit all papers for accuracy, consistency, and readability by specialists and nonspecialists alike.

- **UP-TO-DATE**

Each issue is packed with the latest research findings, reviews, and commentaries, as well as an extensive section offering the latest news on cancer-related science, policy, politics, and people.

The *Journal of the National Cancer Institute* remains the Number 1 journal in the field, publishing the best original research papers in oncology from around the world. Internationally acclaimed as the source of the most up-to-date information and news from the rapidly changing fields of cancer research and treatment, the *Journal of the National Cancer Institute* now carries advertisements.

## CIRCULATION: 7,000

## MARKET AND COVERAGE

Journal readership includes cancer researchers, oncologists, internists, hematology/oncologists, surgeons, physicians, epidemiologists, educators, and policy makers. Subscription distribution: North America, 70%; Europe, 20%; Japan, 4%; rest of world, 6%.

## DISPLAY ADVERTISING RATES (in US$)

**Black-and-White Rates**

| | 1x | 3x | 6x | 12x | 18x | 24x |
|---|---|---|---|---|---|---|
| Full Page, $ | 1420 | 1350 | 1280 | 1205 | 1135 | 1065 |
| Half Page, $ | 975 | 920 | 875 | 825 | 780 | 730 |
| Third Page, $ | 790 | 750 | 710 | 670 | 635 | N.A. |
| Quarter Page, $ | 675 | 645 | 615 | 570 | 540 | N.A. |
| Sixth Page, $ | 510 | 490 | 465 | 445 | 420 | N.A. |

N.A. = Not applicable.

**Additional Charge for Color**

- Standard color: $625 per page or fraction
- Matched color: $700 per page or fraction
- Four color: $1600 per page or fraction

**Cover and Special Position Rates**

- 2nd cover (IFC): 35%
- 3rd cover (IBC): 25%
- Facing contents: 25%
- Facing text: 25%

**Miscellaneous**

- Agency commission: 15%

## MECHANICAL DATA

Unit Sizes:

Spread (2 facing pages), w x h: 14 5/8" x 9 3/4"
Full page size, w x h: 7 5/16" x 9 3/4"
Half page (horizontal) w x h: 7 5/16" x 4 3/4"
Half page (vertical) w x h: 3 1/2" x 9 3/4"
Quarter page size, w x h: 3 1/2" x 4 3/4"

Bleed Sizes:

Trim page size, w x h: 8 1/2" x 11"
Bleed page size: allow 1/4" (3 mm) trim on each bleed edge
Halftone screen: 150 line

**Single- and Two-Color Advertisements**

Please supply same-size, camera-ready artwork or negative film.

**Four-Color Advertisements**

Color-separated negatives and a set of progressive proofs are required. Right-reading, emulsion-side-down films are preferred.

## CLASSIFIED ADVERTISING

Advertisements are now being accepted for employment, awards, grants, fellowships, conferences, symposia, etc. These advertisements are placed at the back of the journal.

**Display Classified Advertising**

Rates for black-and-white reproduction of display advertising are as follows:

- Full page: $1420
- Half page: $975
- Third page: $790
- Quarter page: $675
- Sixth page: $510

Display classified advertisements in camera-ready format, supplied as three original copies of artwork (plus identical artwork on disk) or as film negatives, should be sent to the advertising coordinator at the Journal office (*see* address below).

**All Display Classified Advertisements Must Be Set in a Box Rule**

Full page box, w x h: 7 5/16" x 9 3/4"
Half page box, w x h: 7 5/16" x 4 3/4"
Half page vertical w x h: 3 1/2" x 9 3/4"
Third page box, w x h: 4 11/16" x 4 3/4"
Quarter page box, w x h: 3 1/2" x 4 3/4"
Sixth page box, w x h: 2 1/4" x 4 3/4"

**Copy to Be Set by the *Journal***

As a service to advertisers, the *Journal* can typeset and format display classified advertisements. Fax text and layout guidelines to PRC Associates (*see* address below). Production charges are as follows:

- Full page: $130
- Half page: $115
- Third page: $100
- Quarter page: $100
- Sixth page: $100

## ADVERTISEMENT PREPARATION

Please use American English spellings, unless an alternate spelling is part of a proper name. Be sure to spell check all copy before printing the final version. When preparing full-page display advertising, layout the page for an 8 1/2" x 11" measure. For best appearance, allow sufficient white space between copy and the box rule around the advertisement. When supplying single-color camera-ready artwork for display advertisements, please send three original prints (plus the identical artwork on disk) or send film negatives.

ANTICANCER RESEARCH
International Journal of Cancer Research and Treatment

ISSN: 0250-7005

## ADVERTISING IN ANTICANCER RESEARCH

### Letter from the Managing Editor

Dear Advertiser:

The exceptional success of ANTICANCER RESEARCH is attributed to (a) the superior quality of contents selected by an international Editorial Board consisting of eminent authorities in all fields of oncology, and (b) the rapid publication of all accepted material using the highest technical standards. For these reasons ANTICANCER RESEARCH has been respected and enthusiastically supported all over the world.

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**Editors/Key Personnel:** Nicholas R. Cozzarelli, Editor; Kenneth R. Fulton, Publisher; Diane M. Sullenberger, Executive Ed.

**Founded:** 1915

**Abstract:** Journal of multidisciplinary sciences.

**Language:** English

**Frequency/Update Freq.:** Biweekly
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**Editors/Key Personnel:** Morgan Robinson, Editor, fax (215)440-9355, robinson@aacr.org; Margaret Foti, Managing Editor, foti@aacr.org; Michael Beveridge, Asst. Director of Publications, fax (215)440-9355,beveridge@aacr.org

**Founded:** 1941

**Abstract:** Journal covering clinical and laboratory cancer research.

**Language:** English

**Frequency/Update Freq.:** Semimonthly
**Printing Method:** Offset. **Size:** 8 3/8 x 10 7/8.
**Cols. per Pg.:** 2. **Col. Width:** 42 picas. **Col. Depth:** 126 agate lines.
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**Circulation - paid:** 8,900 ( Publisher's Statement )
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Houston, TX 77030
**Phone:** (713)792-6015
**Fax:** (713)792-6016
E-Mail: aacr@aacr.org
URL: http://www.aacr@org

**Editors/Key Personnel:** John Mendelsohn, Editor-in-Chief

**Founded:** 1994

**Abstract:** Professional medical journal covering clinical research on cancer.

**Language:** English

**Frequency/Update Freq.:** Monthly
**Size:** 8 3/8 x 10 7/8.
**Cols. per Pg.:** 2. **Col. Width:** 3 1/4 inches. **Col. Depth:** 9 inches.
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**ISSN:** 1078-0432

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(signature)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | |
|---|---|
| Petitioner: | Alfacell Corporation |
| Registrant: | Anticancer, Inc. |
| Mark: | ONCASE |
| Reg. No.: | 1,987,445 |
| Cancellation No.: | 32,202 |

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By: _____
Chase Trombella

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE TRADEMARK TRIAL AND APPEAL BOARD

| | |
|---|---|
| Alfacell Corporation<br>Petitioner<br>vs.<br>Anticancer, Inc.<br>Registrant | Cancellation No.: 32,202<br>Registration No. 1,987,445 |



**REGISTRANT ANTICANCER, INC.'S NOTICE OF RELIANCE: WEBSITE OF OPPOSER ALFACELL CORP.**

Pursuant to 37 C.F.R. § 2.122(d)(2) and Rule 703.02(a) of the Trademark Trial and Appeal Board Manual of Procedure, Registrant Anticancer, Inc. ("Registrant") hereby submits this Notice of Reliance during its testimony period. Anticancer is relying upon printouts from the website of Petitioner Alfacell Corp. ("Petitioner").

The printouts from Petitioner's website are relevant because they support the conclusion that Registrant's mark ONCASE is not likely to cause confusion with Petitioner's mark ONCONASE. Specifically, the printouts from Petitioner's website establish that Petitioner's ONCONASE mark was widely promoted. The Board recognizes that under the *Du Pont* likelihood of confusion analysis, a long period of concurrent, simultaneous use of two marks, without any instances of actual confusion is persuasive evidence that there is no likelihood of confusion between the two marks. *Application of E.I. DuPont DeNemours & Co.*, 476 F.2d 1357, 1361, 177 U.S.P.Q. (BNA) 563, 567 (C.C.P.A. 1973); *G.H. Mumm & Cie v. Desnoes & Geddes Ltd.*, 917 F.2d 1292, 16 USPQ2d 1635, 1638 (Fed. Cir. 1990); *Marcal Paper Mills, Inc. v. American Can Company*, 1981 TTAB LEXIS 9 at *39.

The attached printouts from Petitioner's website meet all requirements for admissibility. Printed publications, including electronically generated documents, may be introduced in evidence by a notice of reliance. TBMP § 708; 37 C.F.R. § 2.122(e).

Based upon these authorities, Anticancer respectfully requests that the attached material be admitted in evidence.

Dated: April 11, 2003

Respectfully submitted,

By _____

Jennifer Lee Taylor
Attorney for Registrant

MORRISON & FOERSTER LLP
425 Market Street
San Francisco, California 94105-2482
Telephone: (415) 268-6538
Facsimile: (415) 268-7522

# ALFACELL CORPORATION

*ALFACELL...*
*world leader in RNase therapeutic development*

***ALFACELL Corporation is a biopharmaceutical company engaged primarily in the research and development of novel ribonuclease (RNase) enzymes for various therapeutic applications.***

***ONCONASE®, a novel RNase, is being investigated in a multicenter Phase III trial for patients with malignant mesothelioma (asbestos-related cancer).***

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Refined 1.7Å X-ray Crystallographic Structure of P-30 Protein, an Amphibian Ribonuclease with Anti-tumor Activity. S. C. Mosimann, W. Ardelt and M. N. G. James. ***Journal of Molecular Biology* 236: 1141-1153, 1994.**

Cytotoxic ONCONASE and Ribonuclease A Chimeras: Comparison and *In Vitro* Characterization. S. Rybak, D. Newton, S. Mikulski, A. Viera, R. Youle. ***Drug Delivery* 1: 3-10, 1993.**

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A Cytotoxic Ribonuclease: Study of the Mechanism of ONCONASE Cytotoxicity. Y. Wu, S. Mikulski, W. Ardelt, S. Rybak, R. Youle. ***The Journal of Biological Chemistry* 268: 10686- 10693, 1993.**

Human Tumor Cell Growth Modulatory Effects of the AEBS/$H_{IC}$-binding Drugs Use as Single Agents and in Combination with a Novel Amphibian Oocyte RNase. S. Mikulski, A. Viera, K. Shogen. ***International Journal of Oncology* 2: 807-812, 1993.**

Comparative Molecular Modeling and Crystallization of P-30 Protein: A Novel Antitumor Protein of Rana pipiens Oocytes and Early Embryos. S. Mosimann, K. Johns, W. Ardelt, S. Mikulski, K. Shogen, M. James. ***PROTEINS: Structure, Function and Genetics* 14: 392-400, 1992.**

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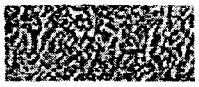

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REVIEW: Natural and Engineered Cytotoxic Ribonucleases: Therapeutic Potential. Susanna M. Rybak and Diane L. Newton. *Experimental Cell Research* 253: 325-335, 1999.

Interferon Enhances the Activity of the Anticancer Ribonuclease, Onconase. Veena M. Vasandani, Joann C. Castelli, Jonathan S. Hott, Shailendra Saxena, Stanislaw M. Mikulski, and Richard J. Youle. ***Journal of Interferon and Cytokine Research* 19: 447-454, 1999.**

Cell Cycle-Related Differences in Susceptibility of NIH/3T3 Cells to Ribonucleases. Mark R Smith, Dianne L Newton, Stanislaw M. Mikulski, and Susanna M. Rybak. ***Experimental Cell Research* 247: 220-232, 1999.**

Enhanced *in vitro* Cytotoxicity and Cytostasis of the Combination of ONCONASE with a Proteasome Inhibitor. Stanislaw M. Mikulski, Alejandro Viera, Andrzej Deptala, and Zbigniew Darzynkiewicz. ***International Journal of Oncology* 13: 633-644, 1998.**

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Enhancement of Vincristine Cytoxicity in Drug-Resistant Cells by Simultaneous Treatment with ONCONASE, an Antitumor Ribonuclease. S. Rybak, J. Pearson, W. Fogler, K. Volker, S. Spence, D. Newton, S. Mikulski, W. Ardelt, C. Riggs, H. Kung, D. Longo. ***Journal of the National Cancer Institute*, Vol. 88: No. 11, 747-753, June 1996.**

Role of the N Terminus in RNase A Homologues: Differences in Catalytic Activity, Ribonuclease Inhibitor Interaction and Cytotoxicity. E. Boix, Y.N. Wu, V.M. Vasandani, S. K. Saxena, W. Ardelt, J. Ladner and R. J. Youle. ***Journal of Molecular Biology*, Vol. 257: 992-1007, April 1996.**

Treatment of malignant mesothelioma (Review). S. Mikulski. ***International Journal of Oncology* 7: 1415-1420, 1995.**

A Study of the Intracellular Routing of Cytotoxic Ribonucleases. Y. Wu, S. Saxena, W. Ardelt, M. Gadina, S. Mikulski, C. De Lorenzo, G. D'Alessio, and R. Youle. ***The Journal of Biological Chemistry* 270: 17476-17481, 1995.**

A novel re-regulator of cancer growth? A Commentary. S. Mikulski. ***Oncology Reports* 2: 797-799, 1995.**

Relationship Between Response Rate and Median Survival in Patients with Advanced Non-Small Cell Lung Cancer: Comparison of ONCONASE® With Other Anticancer Agents. S. Mikulski, H. Chun, A. Mittelman, T. Panella, C. Puccio, K. Shogen, J. Costanzi. ***International Journal of Oncology* 6: 889-897, 1995.**

RNase Inhibition of Human Immunodeficiency Virus Infection of H9 Cells. R. Youle, Y. Wu, S. Mikulski, K. Shogen, R. Hamilton, D. Newton, G. D'Alessio, and M. Gravell. ***Proceedings of the National Academy of Sciences USA* 91: 6012-6016, June 1994.**

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Phase II Trial of a Single Weekly Intravenous Dose of Ranpirnase in Patients with Unresectable Malignant Mesothelioma. Stanislaw M. Mikulski, John J. Costanzi, Nicholas J. Vogelzang, Spemce McCachren, Robert N. Taub, Hoo Chun, Abraham Mittelman, Timothy Panella, Carmelo Puccio, Robert Fine and Kuslima Shogen. ***Journal of Clinical Oncology*, Vol. 20 No. 274-281, January 1, 2002.**

Potent and Specific Antitumor Effects of an Anti-CD22-Targeted Cytotoxic Ribonuclease: Potential for the Treatment of non-Hodgkin Lymphoma. Dianne L. Newton, Hans J. Hansen, Stanislaw M. Mikulski, David M. Goldenberg and Susanna M. Rybak. ***Blood*, Vol. 97: No. 2, 528-535, January 15, 2001.**

Induction of Differentiation of Leukaemic (HL-60) or Prostate Cancer (LNCaP, JCA-1) Cells Potentiates Apoptosis Triggered by Onconase. H. D. Halicka, T. Murakami, C. N. Papageorgio, A. Mittelman, S. M. Mikulski, K. Shogen and Z. Darzynkiewicz. ***Cell Prolif.* 33: 407-417, 2000.**

Tumoricidal Effects of Onconase on Various Tumors. Intae Lee, Young H. Lee, Stanislaw Mikulski, Jihean Lee, Kenneth Covone and Kuslima Shogen. ***Journal of Surgical Oncology* 73: 164-171, 2000.**

Enhanced Cellular Radiation Sensitivity of Androgen-Independent Human Prostate Tumor Cells by Onconase. Intae Lee, Young H. Lee, Stanislaw M. Mikulski, Jihean Lee and Kuslima Shogen. ***Anticancer Research* 20: 1037-1040, 2000.**

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RN321 Onconase Based Targeted Therapeutic. S. M. Rybak, D. L. Newton, K. Shogen, S. M. Mikulski, and E. Sausville. **Sixth International Meeting on Ribonucleases, Bath UK, June 2002.**

Anti-Viral Effects of ONCONASE® (Ranpirnase). M. Michaelis, S. M. Mikulski, K. Shogen, H.W. Doerr, and J. Cinatl, Jr. **Sixth International Meeting on Ribonucleases, Bath UK, June 2002.**

A Novel Cytotoxic Ribonuclease for Amphiban Oocytes. W. Ardelt, E. Vidumas, S. Saxena, H.S. Lee, A Saxena, A. Viera, and K. Shogen. **Sixth International Meeting on Ribonucleases, Bath UK, June 2002.**

Studies on the Substrate Specificity of Onconase. A. N. Suhasini, S. Kumar and R. Sirdeshmukh. **Sixth International Meeting on Ribonucleases, Bath UK, June 2002.**

Onconase and Doxorubicin Synergy in Prolonging Survival of Mda-mb-231 Human Breast Cancer Bearing Nude Mice. S. M. Mikulski, D. L. Newton, R. H. Wiltrout, and, S. M. Rybak. (Abstract #3246) **Presented at the 90th Annual Meeting of the American Association For Cancer Research (AACR), April 1999.**

A New Anti-Cancer RNase (ONCONASE): Preliminary Results in Patients with Breast Cancer. A. Mittelman, C. Puccio, H. Chun, J. Costanzi, T. Panella, N. Coombe, K. Shogen, S. Mikulski. **(Presentation No. 222) the 21st Meeting of the International Association for Breast Cancer Research, July 1996.**

Anti-Tumor Ribonucleases. Characterization of a Natural Variant of ONCONASE. W. Ardelt, H. Lee, G. Randolph, A. Viera, S. Mikulski, K. Shogen. **Presented at the 4th International Meeting on Ribonucleases: Chemistry, Biology, Biotechnology, Groningen (The Netherlands), July 1996.**

Induction of Differentiation and Apoptosis of U937 and HL-60 Cells by ONCONASE: Potentiation by Inhibitors of Protein Kinases. H. D. Halicka, G. Juan, B. Ardelt, A. Mittelman, W. Ardelt, S. Mikulski, K. Shogen, and Z. Darzynkiewicz. **(Abstract #18) ASCO Proceedings, May 1996.**

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# ABOUT ALFACELL

*A ribbon diagram of ONCONASE®, based on the crystallographic three-dimensional structure.*

ALFACELL is dedicated to the research and development of a new family of proteins isolated from the eggs and early embryos of the leopard frog (*Rana pipiens*), which has the potential to create a whole new class of therapeutic compounds. The first protein isolated, was discovered to be a ribonuclease (RNase), and is ALFACELL's first product, ONCONASE®.

## *Overview*

Alfacell's flagship product, ONCONASE® (ranpirnase) was discovered to be a novel ribonuclease with both anti-cancer and anti-viral activities. The Company believes that the discovery of this novel RNase provides a new technology platform from which an entirely new class of therapeutics will be developed.

The First Product in the Pipeline: **ONCONASE® (ranpirnase) for Injection**

## *Research and Development*

The Company's research and development program has focused on the discovery and development of novel amphibian proteins. ONCONASE is a novel RNase possessing cytotoxic activity *in vitro* and *in vivo* and is not inhibited by endogenous mammalian RNase inhibitors. ONCONASE is the first RNase to reach Phase III clinical trials.

The objective of the R&D program is three-fold:

- maximize the further development of ONCONASE;
- continue the discovery of other related novel bioactive compounds and their most effective therapeutic applications;
- maintain a competitive advantage and fully realize the economic potential of its RNase-based technology.

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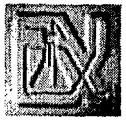

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# CURRENT EVENTS

## *Media Coverage*

ONCONASE® on CNN

## *For the latest news...*

Co-sponsored by Alfacell, The 6th International Conference on Ribonucleases

Conference Banquet Speech from the 6th International Conference on Ribonucleases Presented by Tina Shogen, CEO of Alfacell Corporation (Adobe Acrobat Reader required for viewing.)

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# CONTACT US

## *For More Information*

For Clinical Trial Information please e-mail:
patientinfo@alfacell.com

For Investors/Media Information please e-mail:
InvestorInfo@alfacell.com

For Strategic Alliance Information please e-mail:
kshogen@alfacell.com

For General Information please e-mail: info@alfacell.com

For Website Comments please e-mail: webmaster@alfacell.com

**Mailing Address:**

**Alfacell Corporation**

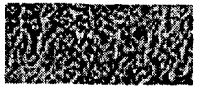
**225 Belleville Avenue**

**Bloomfield, NJ 07003**

**Telephone: (973)-748-8082**

**Fax: (973)-748-1355**

General email: Info@Alfacell.com



# Alfacell Literature and Links

Related Links

Research Presentations

Publications 2000 to 2002

Publications 1995 to 1999

Publications 1988 to 1994

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## *Press Releases*

**All press releases and other information listed below were, to the best of Alfacell's knowledge, timely and accurate when issued. However, the passage of time can render information stale, and you should not rely on the continued accuracy of any such material beyond the date of issuance. Alfacell has no responsibility to update any information contained in any such material. All viewers should carefully check the dates of issuance of the material contained in the Alfacell site.**

## *2002*

**September 19, 2002 - Alfacell and National Cancer Institute (NCI) Expand Research Collaboration**

**August 18, 2002 - Alfacell Awarded New Patent For Methodology of Manufacture/Cloning Synthetic Genes for Ranpirnase and Variant**

**July 9, 2002 Alfacell Expands its Proprietary Ribonuclease-based Product Pipeline**

**May 2, 2002 New Findings Further Illustrate ONCONASE's Mechanism of Action as a Potential Anti-Viral Agent in HIV-1**

**April 15, 2002 Alfacell Announces Growing Incidence of Malignant Mesothelioma and its Treatment to be Addressed at International Investigators' Meeting**

**April 10, 2002 Alfacell's ONCONASE® Significantly Inhibits RNA Viruses Including HIV-1**

**April 4, 2002 Alfacell Provides Update on its Phase III Program of ONCONASE® for the Treatment of Patients with Unresectable Malignant Mesothelioma**

**February 7, 2002 Alfacell Retains Roan/Meyers Associates for Investment Banking Services**

**January 29, 2002 New Collaborative Research Program between Alfacell and University of Frankfurt**

**January 22, 2002 Encouraging Survival in Patients with advanced Malignant Mesothelioma Treated with Alfacell's ONCONASE®**

## *2001*

**July 10, 2001 ONCONASE® is available in Europe to Patients with Malignant Mesothelioma**

**June 28, 2001 New Novel Anti-Cancer protein Discovered by Alfacell Scientists**

**May 21, 2001 Alfacell Corporation Announces Extension of Warrants**

**February 14, 2001 Alfacell Receives New U.S. Patent and Broadens Relationship with the National Cancer Institute**

**February 14, 2001 Alfacell Corporation's ONCONASE® Receives Orphan Medicinal Product Designation**

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Corporation
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# ABOUT ALFACELL

***Research and Development Program***

## ALFACELL'S PRODUCT CANDIDATES*

| *THERAPEUTIC AREA* | *PRODUCT* | *INDICATION* | *PHASE* | *STATUS* |
|---|---|---|---|---|
| ***ONCOLOGY*** | ONCONASE | Malignant Mesothelioma | II | COMPLETED |
| ***ONCOLOGY*** | ONCONASE | Malignant Mesothelioma | III | COMPLETED |
| ***ONCOLOGY*** | ONCONASE + doxorubicin | Malignant Mesothelioma | III | ONGOING |
| ***ONCOLOGY*** | ONCONASE | Refractory Breast | II | COMPLETED |
| ***ONCOLOGY*** | ONCONASE + tamoxifen | Renal Cell | II | COMPLETED |
| ***ONCOLOGY*** | ONCONASE + α-INF + Oral 13-Cis- Retinoic Acid | Renal Cell | I | COMPLETED |
| ***ONCOLOGY*** | ONCONASE + tamoxifen | Prostate | II | COMPLETED |

| *THERAPEUTIC AREA* | *PRODUCT* | *INDICATION* | *PHASE* | *STATUS* |
|---|---|---|---|---|
| ***TARGETED THERAPY*** | RN321 | NHL | PRECLINICAL | ONGOING |
| ***TARGETED THERAPY*** | Genetically Engineered Ranpirnase Payload & Fusion Protein(s) | Variety of Indications | PRECLINICAL | ONGOING |
| ***TARGETED THERAPY*** | Ranpirnase | Radiosensitizing & Anti-Angiogenic Agent | PRECLINICAL | ONGOING |

| | | | | |
|---|---|---|---|---|
| ***TARGETED THERAPY*** | Ribonuclease Variants | Broad Spectrum Of Cancers | PRECLINICAL | ONGOING |
| ***TARGETED THERAPY*** | Proteasome inhibitors | Broad Spectrum Of Cancers | PRECLINICAL | ONGOING |
| ***ANTI VIRAL*** | Ranpirnase | HIV + Other Indications | PRECLINICAL | ONGOING |
| ***GENE THERAPY*** | Genes of Ranpirnase and of other variants | Broad Spectrum Of Cancers | PRECLINICAL | ONGOING |

***This document is intended to provide an overview of Alfacell's product candidates, for complete information refer to the company's Form 10-K.**

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# ABOUT ALFACELL

## *Research Collaborations*

**National Institutes of Health (NIH) Sponsored Programs**

ONCONASE has shown promising activity *in vitro* against the HIV-1 virus, the causative agent of AIDS. Alfacell is seeking a strategic partner to co-develop ONCONASE as anti-viral agent.

**National Cancer Institute (NCI) Sponsored Programs**

NCI-sponsored clinical trials with the RN321 conjugate for patients with non-Hodgkin's lymphoma are planned. Synergisms between ranpirnase and soluble *fas* ligands (sFasL) are being studied in human resistant tumors.

**University Collaborations have been or are ongoing with:**

- *University of Pennsylvania, Philadelphia, Pennsylvania*
- *Harvard University, Boston, Massachusetts*
- *University of Rhode Island, Providence, Rhode Island*
- *New York Medical College, Valhalla, New York*
- *Institute of Medicinal Virology at Johann Wolfgang University of Frankfurt, Germany*
- *University Degli Studi G.D. Annunzio, Chieti, Italy*

**Requests for potential collaborations with Alfacell can be**

**made to Kshogen@Alfacell.com or 1-888 Alfacell (253-2235)**

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# ABOUT ALFACELL

## *Strategic Alliances*

Alfacell has recognized the importance of laying the groundwork for marketing early in the product development cycle.

Carefully planned strategic research collaborations are essential building blocks for credibility and recognition in the oncology field. Alfacell has long standing collaborations with the National Institutes of Health, including NCI, and other major academic and cancer centers worldwide..

Alfacell intends to form partnership(s) with established companies with existing sales and marketing structure.

In order to develop a global marketing plan for the Company's technology, partners with expertise and a proven track-record in the four major geographical areas are being sought.

- The United States and Canada
- Europe
- Japan/Pacific Rim (including Australia)

- Latin America

**Interested parties should contact Alfacell at Kshogen@Alfacell.com or 1-888 Alfacell (253-2235)**

**Patents**

Alfacell owns 10 patents in the United States and four European patents, which have been validated in certain European countries.

Additional patent applications are pending in the United States, Europe, and Japan.

Alfacell owns one Japanese patent and has an undivided interest in two applications that are pending in the United States. Each of these applications relate to a Subject Invention (as that term is defined in Cooperative Research and Development Agreements, or CRADAs, to which Alfacell and the National Institutes of Health are parties).

**Trademarks/USAN/INN**

The ONCONASE trademark has been registered in the U.S. and other selected countries.

The United States Adopted Names Council (USAN) name ranpirnase was adopted in May 1998, and the World Health Organization (WHO) approved ranpirnase as the International Non-proprietary Name (INN) on October 28, 1998.

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# ABOUT ALFACELL

## *Corporate Profile*

**Employees:** 15 full-time, Number of PhDs: 3, Number of MDs: 1

**Alfacell Management:**

Kuslima Shogen, *Chief Executive Officer, Co-Founder*

Stanislaw M. Mikulski, M.D., F.A.C.P., *Executive Vice President and Medical Director*

**Board of Directors:**

Kuslima Shogen, *Chairman of the Board*

Stanislaw M. Mikulski, M.D., F.A.C.P., *Director*

Stephen K. Carter, M.D., *Director*
Former Senior Vice President, Clinical R&D
Bristol-Myers Squibb Pharmaceuticals

Donald R. Conklin, *Director*
Former President of Schering-Plough Pharmaceuticals

Martin F. Stadler, *Director*
Former Chief Financial Officer of Hoffman La-Roche, Inc.

**Scientific Advisory Board:**

Stephen K. Carter, M.D.
*Chairman*

John J. Costanzi, M.D.
Former Professor of Medicine and Director of the
Cancer Center for the University of Texas

Zbigniew Darzynkiewicz, M.D., Ph.D.
Director of the Brander Cancer Research Institute,
New York Medical College

Abraham Mittelman, M.D.
Professor of Medicine and Associate Director of Oncology,
New York Medical College

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## *INVESTORS INFORMATION*

**Get more investment information...**

**Trading Symbol:**
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**Exchange:**
OTC Bulletin Board

**Stock Quote:**
Current Stock Quote

**SEC Filings:**
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| Your last name | |
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| Company Name or Affiliation (if applicable) | |
| Address | |
| | |
| City | |
| State | |
| Zip/Post Code | |
| Country (other than U.S.) | |
| Phone Number (with area code) | |
| Fax Number (with area code) | |
| E-mail address | |

Are you a:

| | | |
|---|---|---|
| ○ Shareholder | ○ Analyst | ○ Investment Banker |
| ○ Potential Investor | ○ Media Contact | ○ Stockbroker |

○ Scientist ○ Other (please specify): _____

How did you hear about Alfacell?

○ Physician ○ Patient Referral ○ Link from Other Site

○ Internet Search ○ Publication (Please list): _____

○ Newsgroup ○ Word of Mouth

○ Other Source (Please list): _____

How did you find this site?

○ Search Engine ○ Newsgroup ○ Word of Mouth

○ Physician ○ Link from Other Site

○ Other Source (Please list): _____

Would you like to be notified by email of future updates to the website?

◉ Yes ○ No

Please send more information:

☐ Annual Report ☐ Proxy

☐ Publications ☐ Research (Analyst) Report(s)

☐ Other: _____

Other Comments:

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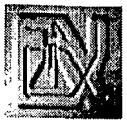

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**Alfacell Corporation**

| | | | |
|---|---|---|---|
| Last | **0.60** | Open | 0.64 |
| Change | -0.03 | Previous Close | 0.63 |
| % Change | -4.76% | Bid | 0.60 |
| Volume | 18,800 | Ask | 0.65 |
| Avg Daily Volume | NA | Instit. Ownership | NA |
| Day's High | 0.64 | 52 Week High | 1.01 |
| Day's Low | 0.60 | 52 Week Low | 0.18 |
| StockScouter Rating | NA | Intraday Chart | |

**Fundamental Data**

| | | | |
|---|---|---|---|
| P/E | NA | Market Cap. | NA |
| Earnings/Share | NA | # Shares Out. | NA |
| Dividend/Share | NA | Exchange | OTC BB |
| Current Div. Yield | NA | Stock Alerts \| Message Board | |

Last trade 01:19 PM ET
Financial data in U.S. dollars



## News & Analysis

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## *Search Results* [redacted]

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| Date | Filings | More Info |
|---|---|---|
| Apr 9 2003 | **ALFACELL CORP** SC 13D/A: Amended Ownership Statement | Hard Copy , Premium Research, People, Real Time Quote , Company Dossier, Financials, Delayed Quote, Chart, IPO Express, Annual Report |
| Mar 17 2003 | **ALFACELL CORP** 10-Q: Quarterly Report | Hard Copy , Premium Research, Glimpse, People, Real Time Quote , Company Dossier, Financials, Delayed Quote, Chart, IPO Express, Annual Report |
| Mar 11 2003 | **ALFACELL CORP** 424B1: Omitted Information From Original Registration Statement | Hard Copy , Premium Research, People, Real Time Quote , Company Dossier, Financials, Delayed Quote, Chart, IPO Express, Annual Report |
| Mar 11 2003 | **ALFACELL CORP** 424B1: Omitted Information From Original Registration Statement | Hard Copy , Premium Research, People, Real Time Quote , Company Dossier, Financials, Delayed Quote, Chart, IPO Express, Annual Report |
| Mar 3 2003 | **ALFACELL CORP** POS AM: Post-Effective Amendment | Hard Copy , Premium Research, People, Real Time Quote , Company Dossier, Financials, Delayed Quote, Chart, IPO Express, Annual Report |
| Mar 3 2003 | **ALFACELL** | Hard Copy , Premium Research, People, Real Time Quote , Company Dossier, Financials, |

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| | **CORP** POS AM: Post-Effective Amendment | Delayed Quote, Chart, IPO Express, Annual Report ♣ |
| Feb 5 2003 | **ALFACELL CORP** 3: Initial Filing of Equity Securities | Hard Copy , Premium Research, People, Real Time Quote , Company Dossier, Financials, Delayed Quote, Chart, IPO Express, Annual Report ♣ |
| Feb 4 2003 | **ALFACELL CORP** 8-K: Report of Unscheduled Material Events | Hard Copy , Premium Research, People, Real Time Quote , Company Dossier, Financials, Delayed Quote, Chart, IPO Express, Annual Report ♣ |

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# ABOUT ALFACELL

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Director, Clinical and Regulatory Operations
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Fax: (973) 748-9788
Physican E-mail: PatientInfo@alfacell.com
Patient E-Mail: PatientInfo@alfacell.com

**For Investors, Potential Investors and Media:**
Investor Relations Department
Phone: (973) 748-8082
Fax: (973) 748-1355
Investors/Media E-Mail: InvestorInfo@alfacell.com

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## PROOF OF SERVICE BY OVERNIGHT DELIVERY

I declare that I am employed with the law firm of Morrison & Foerster LLP, whose address is 425 Market Street, San Francisco, California, 94105; I am not a party to the within cause; I am over the age of eighteen years and I am readily familiar with Morrison & Foerster's practice for collection and processing of correspondence for overseas delivery and know that in the ordinary course of Morrison & Foerster's business practice the document described below will be deposited in a box or other facility regularly maintained by UPS or delivered to an authorized courier or driver authorized by UPS to receive documents on the same date that it is placed at Morrison & Foerster for collection.

I further declare that on the date hereof I served a copy of:

**Registrant Anticancer, Inc.'s Notice of Reliance: Website of Opposer Alfacell Corp.**

on the following by placing a true copy thereof enclosed in a sealed envelope with delivery fees provided for, addressed as follows for collection by UPS at Morrison & Foerster LLP, 425 Market Street, San Francisco, California, 94105, in accordance with Morrison & Foerster's ordinary business practices:

Mark H. Jay, Esq.
Mark H. Jay, P.A.
71 Baltusrol Way
Short Hills, NJ 07078-2457

I declare under penalty of perjury under the laws of the State of California that the above is true and correct.

Executed at San Francisco, California, this 11th day of April, 2003.

Lucia M. Sario

(signature)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | |
|---|---|
| Petitioner: | Alfacell Corporation |
| Registrant: | Anticancer, Inc. |
| Mark: | ONCASE |
| Reg. No.: | 1,987,445 |
| Cancellation No.: | 32,202 |

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Trademark Trial and Appeal Board
Assistant Commissioner for Trademarks
2900 Crystal Drive
Arlington, VA 22202-3513

Dear Sir:

Express Mail Label No.: EV 240722497 US

Date of Deposit: April 11, 2003

I hereby certify that the attached **Registrant Anticancer, Inc.'s Notice of Reliance: Website of Opposer Alfacell Corp.,; Registrant Anticancer, Inc.'s Notice of Reliance: Printouts from Website of The Center for Drug Evaluation and Research; Registrant Anticancer, Inc.'s Notice of Reliance: Printouts from Website of The Office of Drug Safety; Registrant Anticancer, Inc.'s Notice of Reliance: Article from The Journal Pharmaceutical Executive; Websites Showing The Circulation of Various Scientific Journals** and receipt verification postcard are being deposited with the United States Postal Service Express Mail delivery as "Express Mail Post Office to Addressee" service under 37 C.F.R § 1.10 on the date indicated above, and is addressed to: Trademark Trial and Appeal Board, Assistant Commissioner for Trademarks, 2900 Crystal Drive, Arlington, VA 22202-3513.

Respectfully submitted,

By: _____

Chase Trombella

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE TRADEMARK TRIAL AND APPEAL BOARD

| | |
|---|---|
| Alfacell Corporation | Cancellation No.: 32,202 |
| Petitioner | Registration No. 1,987,445 |
| vs. | |
| Anticancer, Inc. | |
| Registrant | |



**REGISTRANT ANTICANCER, INC.'S NOTICE OF RELIANCE: PRINTOUTS FROM WEBSITE OF THE OFFICE OF DRUG SAFETY**

Pursuant to 37 C.F.R. § 2.122(d)(2) and Rule 703.02(a) of the Trademark Trial and Appeal Board Manual of Procedure, Registrant Anticancer, Inc. ("Registrant") hereby submits this Notice of Reliance during its testimony period. Anticancer is relying upon printouts from the website of the Office of Drug Safety ("ODS"), which is an Office within the Center for Drug Evaluation and Research ("CDER"). The CDER is part of the Federal Drug Administration ("FDA").

The printouts from ODS's website are relevant because they support the conclusion that Registrant's mark ONCASE is not likely to cause confusion with Petitioner Alfacell Corp.'s ("Petitioner") mark ONCONASE. Given the complexity of the drug approval process, it is unlikely that both trademarks will be used in the market other than in connection with preclinical and clinical trials. Specifically, the printouts from ODS's website establish that the FDA engages in an independent process, separate from that of the United States Patent and Trademark Office, to determine the likelihood of confusion between two drug trademarks, after each drug has passed the rigorous drug application process. Both Registrant's ONCASE product and Petitioner's ONCONASE product are at very early stages in the application process, and therefore, the FDA may

still deny either or both the use of their trademarks when and if each product is approved as a new drug.

The attached printouts from ODS's website meet all requirements for admissibility. Printed publications, including electronically generated documents, may be introduced in evidence by a notice of reliance. TBMP § 708; 37 C.F.R. § 2.122(e).

Based upon these authorities, Anticancer respectfully requests that the attached material be admitted in evidence.

Dated: April 11, 2003

Respectfully submitted,

By _____

Jennifer Lee Taylor
Attorney for Registrant

MORRISON & FOERSTER LLP
425 Market Street
San Francisco, California 94105-2482
Telephone: (415) 268-6538
Facsimile: (415) 268-7522

U.S. Food and Drug Administration • Center for Drug Evaluation and Research

# Office of Drug Safety

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## Office of Drug Safety Divisions

In 2002, the Office of Post-marketing Drug Risk Assessment (OPDRA) was renamed the Office of Drug Safety (ODS), and is now located under a new super office, the Office of Pharmacoepidemiology and Statistical Science (OPaSS). The Office of Drug Safety has gained the MedWatch program, formerly with the Office of Training and Communications, and patient labeling and risk communication functions, formerly with the Division of Drug Marketing, Advertising, and Communications.

ODS will be involved in many Center initiatives dealing with risk management. These will include the development of a Risk Management White Paper, the identification of a risk management and risk communication research agenda and the launch and utilization of the new Drug Safety and Risk Management Advisory Advisory Committee. This new advisory committee is comprised of nationally recognized experts in the areas of risk perception, risk management, pharmacoepidemiology, clinical pharmacology, clinical research, and medication errors. They will advise FDA on both general and product-specific safety issues.

ODS has three divisions.

**Division of Drug Risk Evaluation (DDRE)**

DDRE staff includes safety evaluators whose primary role is to detect and assess safety signals for all marketed drug products. They work closely with medical reviewers in the Office of New Drugs so that potential safety signals are placed in the context of existing preclinical, clinical, or pharmacologic knowledge of the drugs in question.

Our epidemiologists review epidemiologic study protocols that are increasingly

required of manufacturers as phase four commitments. They evaluate various postmarketing surveillance tools that may be incorporated into risk management strategies, such as patient registries and restricted distribution systems. They estimate the public health impact of safety signals by evaluating computerized databases and the published literature.

**Division of Medication Errors and Technical Support (DMETS)**

DMETS primarily provides pre-marketing reviews of all proprietary names, labels and labeling in CDER in order to reduce the medication error potential of a proposed product. DMETS also provides post-marketing review and analysis of all medication errors CDER receives.

**Division of Surveillance, Research, and Communication Support (SRCS)**

SRCS is a newly formed division that handles data resources, risk communication, and outcomes and effectiveness research components of drug safety risk management programs. This Division oversees MedWatch, risk communication research and activities such as Medications Guides, Patient Packet Inserts, and pharmacy information surveys, and international regulatory liaison activities (such as videoconferencing) for all drug and biologic postmarketing safety issues. SRCS also manages the expansion in the use and number of ODS safety and epidemiologic data resources.

Back to Top  Office of Drug Safety

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**FDA/Center for Drug Evaluation and Research**
**Last Updated: October 16, 2002**
**Originator: OTCOM/ODS**
**HTML by SJW**

U.S. Food and Drug Administration • Center for Drug Evaluation and Research

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## Office of Drug Safety



### Introduction

CDER evaluates the safety profiles of drugs available to American consumers using a variety of tools and disciplines throughout the life cycle of the drugs. We maintain a system of postmarketing surveillance and risk assessment programs to identify adverse events that did not appear during the drug development process. We learn about adverse events through required reporting by companies and through voluntary reports submitted to FDA's MedWatch program, which together total more than 250,000 reports per year. Staff in the Office of Drug Safety use this information to identify drug safety concerns and recommend actions to improve product safety and protect the public health. Activities include updating drug labeling, providing more information to the community, implementing or revising a risk management program, and, on rare occasions, reevaluating approval or marketing decisions. CDER also works with drug companies to reduce medication errors related to confusing labels, labeling, drug packaging, and drug names that look alike or sound alike.

### Office of Drug Safety Organization and Responsibilities

- Office of Drug Safety Divisions consists of three divisions.
  - Division of Drug Risk Evaluation,
  - Division of Medication Errors and Technical Support, and
  - Division of Surveillance, Research, and Communication Support

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## Programs and Activities

- Patient Labeling and Risk Communication.

- Drug Safety and Risk Management (DSaRM) Advisory Committee gained full committee status on June 1, 2002.
  - FDA Talk Paper: New Advisory Committee created for Drug Safety and Risk Management. (Posted 12/18/2001)

  - Meeting, member, and charter information for the DSaRM Advisory Committee.

- MedWatch. MedWatch, the FDA Safety Information and Adverse Event Reporting Program, provides safety information for all FDA-regulated medical products (drugs, biologics, medical devices, and dietary supplements) to both healthcare professionals and the general public.
  - MedWatch Partners work with the FDA to help keep their members informed about medical product safety information.

## Regulations, Guidances and MaPPs

- Regulations and Guidances. This web page provides
  - links to Federal regulations regarding postmarketing safety reporting, Medication Guides, draft and final guidance documents.

  - Information on submitting adverse events and safety reports to FDA,

  - Policies and procedures related to drug safety

## Publications

- Publications from the Office of Drug Safety Staff, 1999-2001
- Office of Drug Safety Annual Report 2001

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## Information on Using Medications Safely

- Consumer Drug Information Sheets. Includes sections on who should not use a drug, special warnings, general precautions, and possible side effects. Only information about drugs approved since January 1998 appears on this page.
- FDA Just The Facts: Improving Public Health: Promoting Safe and Effective Drug Use.
- Consumer Education: What You Should Know About Buying and Using Drug Products
- Patient Labeling and Risk Communication.
- Patient Package Inserts.
- Medication Guides.
- Drug Interactions: What You Should Know.
- FDA Consumer magazine articles on drug safety
  - Accutane Risk Management Program Strengthened.
  - Why Drugs Get Pulled Off the Market.
  - Pregnancy and the Drug Dilemma.
  - Prescription Drug Use and Abuse.

- When is a Medical Product Too Risky?

## Other Resources

- Adverse Event Reporting System (AERS).
- Medication Errors web page.
- Report to the Nation: Drug Safety and Quality.

## How to Contact Us

We ask you to take time to communicate with CDER about this web site. Please use our comments form.

Back to Top Divisions and Offices

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**FDA/Center for Drug Evaluation and Research**
**Last Updated: October 23, 2002**
**Originator: OTCOM/ODS**
**HTML by SJW**

## PROOF OF SERVICE BY OVERNIGHT DELIVERY

I declare that I am employed with the law firm of Morrison & Foerster LLP, whose address is 425 Market Street, San Francisco, California, 94105; I am not a party to the within cause; I am over the age of eighteen years and I am readily familiar with Morrison & Foerster's practice for collection and processing of correspondence for overseas delivery and know that in the ordinary course of Morrison & Foerster's business practice the document described below will be deposited in a box or other facility regularly maintained by UPS or delivered to an authorized courier or driver authorized by UPS to receive documents on the same date that it is placed at Morrison & Foerster for collection.

I further declare that on the date hereof I served a copy of:

**Registrant Anticancer, Inc.'s Notice of Reliance: Printouts frojm Website of The Office of Drug Safety**

on the following by placing a true copy thereof enclosed in a sealed envelope with delivery fees provided for, addressed as follows for collection by UPS at Morrison & Foerster LLP, 425 Market Street, San Francisco, California, 94105, in accordance with Morrison & Foerster's ordinary business practices:

Mark H. Jay, Esq.
Mark H. Jay, P.A.
71 Baltusrol Way
Short Hills, NJ 07078-2457

I declare under penalty of perjury under the laws of the State of California that the above is true and correct.

Executed at San Francisco, California, this 11th day of April, 2003.

Lucia M. Sario

(signature)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | |
|---|---|
| Petitioner: | Alfacell Corporation |
| Registrant: | Anticancer, Inc. |
| Mark: | ONCASE |
| Reg. No.: | 1,987,445 |
| Cancellation No.: | 32,202 |

**CERTIFICATE OF MAILING BY EXPRESS MAIL**

Trademark Trial and Appeal Board
Assistant Commissioner for Trademarks
2900 Crystal Drive
Arlington, VA 22202-3513

Dear Sir:

Express Mail Label No.: EV 240722497 US

Date of Deposit: April 11, 2003

I hereby certify that the attached **Registrant Anticancer, Inc.'s Notice of Reliance: Website of Opposer Alfacell Corp.,; Registrant Anticancer, Inc.'s Notice of Reliance: Printouts from Website of The Center for Drug Evaluation and Research; Registrant Anticancer, Inc.'s Notice of Reliance: Printouts from Website of The Office of Drug Safety; Registrant Anticancer, Inc.'s Notice of Reliance: Article from The Journal Pharmaceutical Executive; Websites Showing The Circulation of Various Scientific Journals** and receipt verification postcard are being deposited with the United States Postal Service Express Mail delivery as "Express Mail Post Office to Addressee" service under 37 C.F.R § 1.10 on the date indicated above, and is addressed to: Trademark Trial and Appeal Board, Assistant Commissioner for Trademarks, 2900 Crystal Drive, Arlington, VA 22202-3513.

Respectfully submitted,

By: _____
Chase Trombella

TTAB

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE TRADEMARK TRIAL AND APPEAL BOARD

| | |
|---|---|
| Alfacell Corporation | Cancellation No.: 32,202 |
| Petitioner | Registration No. 1,987,445 |
| vs. | |
| Anticancer, Inc. | |
| Registrant | |





**REGISTRANT ANTICANCER, INC.'S NOTICE OF RELIANCE: ARTICLE FROM THE JOURNAL PHARMACEUTICAL EXECUTIVE**

Pursuant to 37 C.F.R. § 2.122(d)(2) and Rule 703.02(a) of the Trademark Trial and Appeal Board Manual of Procedure, Registrant Anticancer, Inc. ("Registrant") hereby submits this Notice of Reliance during its testimony period. Anticancer is relying upon a journal article entitled "The Name Game: New Realities at FDS," written by Jerry Phillips, RPh, which appeared in the July 2000 issue of the journal *Pharmaceutical Executive.*

The article "The Name Game: New Realities at FDS," is relevant because it supports the conclusion that Registrant's mark ONCASE is not likely to cause confusion with Petitioner Alfacell Corp.'s ("Petitioner") mark ONCONASE. Given the complexity of the drug approval process, it is unlikely that both trademarks will be used in the market other than in connection with preclinical and clinical trials. Specifically, the article, written by a member of the office charged with approving drug trademarks within the FDA, establishes that the FDA engages in an independent process, separate from that of the United States Patent and Trademark Office, to determine the likelihood of confusion between two drug trademarks, after each drug has passed the rigorous drug application process. Both Registrant's ONCASE product and Petitioner's ONCONASE product are at very

early stages in the application process, and therefore, the FDA may still deny either or both the use of their trademarks when and if each product is approved as a new drug.

The attached article meets all requirements for admissibility. Printed publications, including electronically generated documents, may be introduced in evidence by a notice of reliance. TBMP § 708; 37 C.F.R. § 2.122(e).

Based upon these authorities, Anticancer respectfully requests that the attached material be admitted in evidence.

Dated: April 11, 2003

Respectfully submitted,

By _____

Jennifer Lee Taylor
Attorney for Registrant

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Facsimile: (415) 268-7522

# The Name Game

## New Realities at FDA

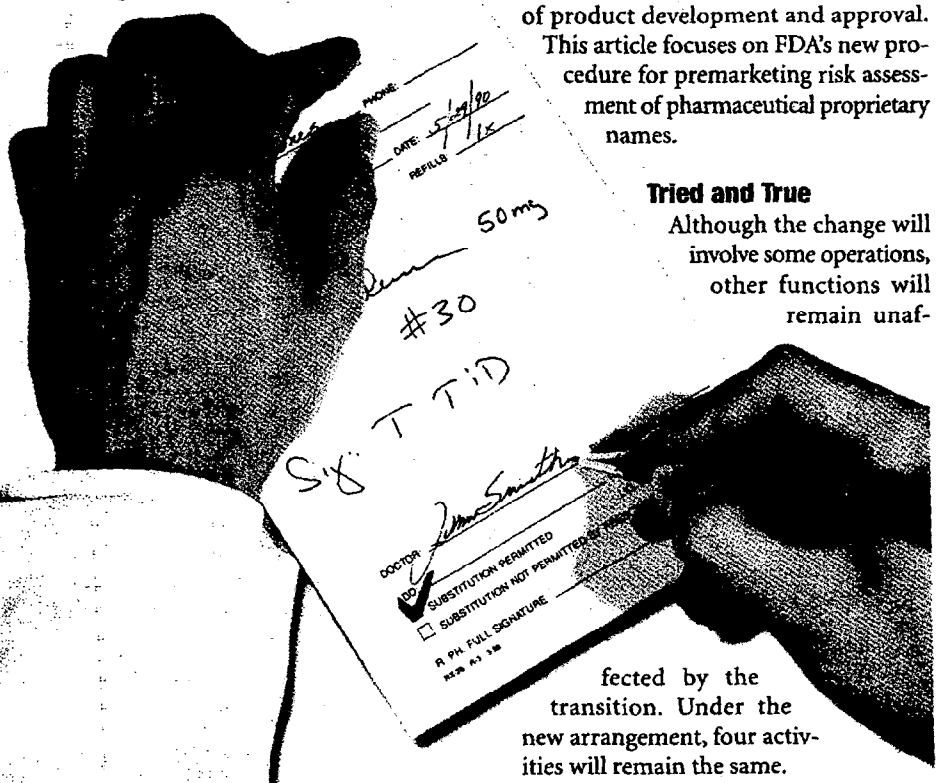
Jerry Phillips

A NEW INITIATIVE SEEKS TO REDUCE MEDICATION ERRORS THROUGH IN-DEPTH PRODUCT NAME REVIEW.

The Center for Drug Evaluation and Research (CDER) at FDA opened a new chapter in proprietary name evaluation for pharmaceutical products when it shifted primary responsibility for that activity to the Office of Post-Marketing Drug Risk Assessment (OPDRA) on 15 October 1999. Previously, CDER's Labeling and Nomenclature Committee (LNC) was responsible for the name evaluation process.

The change in name review activities, designed to minimize medication errors linked to look-alike or sound-alike proprietary names, is part of a larger FDA initiative to improve the agency's ability to manage safety risks across a broad range of responsibilities. OPDRA was formed, in part, to evaluate risk management practices throughout the healthcare delivery system, especially with regard to the roles and responsibilities of FDA.

The name review process at OPDRA, like other regulatory activities there, is designed to bring safety risk assessment to both the pre- and postmarketing phases of product development and approval. This article focuses on FDA's new procedure for premarketing risk assessment of pharmaceutical proprietary names.




CORBIS IMAGES

### Tried and True

Although the change will involve some operations, other functions will remain unaffected by the transition. Under the new arrangement, four activities will remain the same.

**Role of reviewing divisions.** The Office of Review Management's 15 divisions

**Jerry Phillips, RPh,** is associate director for medication error prevention at FDA's Office of Post-Marketing Drug Risk Assessment.

and the Office of Generic Drugs will continue to be the point of contact and source of primary regulatory decisions on proprietary name matters. OPDRA will provide a uniform consultative safety risk assessment and make recommendations, but the primary decision on the suitability of proprietary names rests with the responsible reviewing division director or Office of Drug Evaluation director, as appropriate. Decisions can be appealed through CDER's formal procedures.

**Proprietary names review.** The reviewing division will forward all new proprietary names on new drug applications (NDAs), abbreviated new drug applications (ANDAs), and supplemental new drug applications (SNDAs) to OPDRA for a safety risk assessment.

**Appeals availability.** Pharmaceutical companies will still be able to informally appeal a negative OPDRA recommendation, but that appeal should be made to the reviewing division rather than directly to OPDRA. Informal appeals should be based on persuasive evidence that is relevant to the concerns raised by OPDRA's risk assessment evaluation. In most cases, an OPDRA representative will attend such meetings along with reps from the companies and the reviewing divisions.

**Biologic product deferral.** Products that are regulated by the Center for Biologics Evaluation and Review (CBER) will not normally be sent to OPDRA for proprietary name evaluation. CBER's advertising, promotion, and labeling staff (APLS) will usually evaluate those names.

## Nouveau Approach

OPDRA's new systems approach for proprietary name evaluation also involves new procedures. (See "New Paths.") Those changes reflect the agency's interest in facilitating the safe use of pharmaceutical products prior to approval for consumer use.

Name evaluations will now be available from the conclusion of Phase II through the remainder of the clinical development process. The proposed package insert labeling and visual representation(s) of proposed labels that will be used for the container/carton should accompany the request for name review. In addition, applicants may submit supporting studies and data with the proposed proprietary name for FDA review. Under normal circumstances, that essential preliminary information is unavailable until after the completion of Phase II and the start of Phase III of the clinical research process. CDER encourages companies to submit proposed proprietary names as soon as possible after the end of Phase II trials, but neither rewards companies for submitting names early nor penalizes them for submitting names late.

At present, all proposed proprietary names receive a comprehensive first evaluation requiring about 60 days to complete. Those found acceptable in the first evaluation will receive a second evaluation about 90 days before NDA approval. In the second evaluation, OPDRA narrows its focus to products that have been approved since the first review, ensuring that recent FDA approvals are acceptably dissimilar in sight and sound from the proprietary name under consideration. The second review, because of its narrow scope, will be completed in less than 30 days. Contingencies in approval for the product itself—such as requirements for additional data—may lengthen the time of the second review.

*Continued*

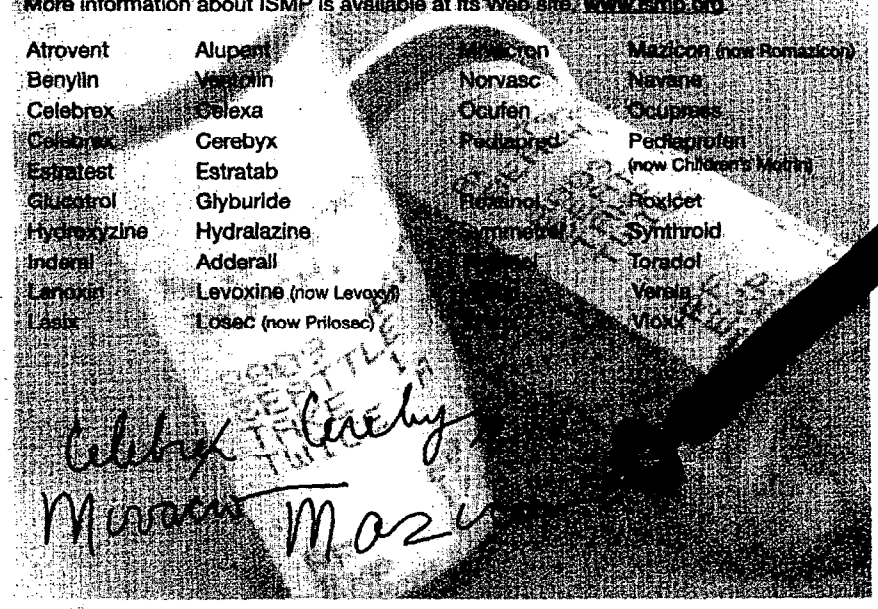
## Troublesome Trademarks

The Institute for Safe Medication Practices (ISMP), a nonprofit health advocacy organization, routinely alerts doctors and pharmacists to the potential risks of certain pairs of pharmaceutical trademarks. One of its missions is to render actual errors, barely avoided problems, and safety concerns reported by a few practitioners into broad-based educational efforts for large numbers of practitioners. The goal is to reduce or eliminate patient harm by alerting the healthcare community to potential problems that could lead to medication errors.

**Similarity in sight or sound of drug names can create possible patient harm.**

One source of medication errors is trademark pairs that are sufficiently similar in sight or sound that they create some degree of confusion and therefore possible patient harm. Listed here are pairs of trademarks that have been reported to the USP Medication Error Reporting Program (MERP) or FDA's MedWATCH program, or have appeared in the ISMP *Medication Error Safety* newsletter that is faxed to virtually all hospitals in the United States. Each of the pairs has been the subject of an educational message in the newsletter, articles in professional journals, or the book, "Medication Errors," written by ISMP president Michael Cohen and published by the American Pharmaceutical Association. More information about ISMP is available at its Web site, www.ismp.org.

| | |
|---|---|
| Atrovent | Alupent |
| Benylin | Ventolin |
| Celebrex | Celexa |
| Celebrex | Cerebyx |
| Estratest | Estratab |
| Glucotrol | Glyburide |
| Hydroxyzine | Hydralazine |
| Inderal | Adderall |
| Lanoxin | Levoxine (now Levoxyl) |
| Lasix | Losec (now Prilosec) |
| Micronor | Modicon (now Romazicon) |
| Norvasc | Navane |
| Ocufen | Ocupress |
| Pediapred | Pediaprofen (now Children's Motrin) |
| Rythmol | Roxicet |
| Synthroid | Synthroid |
| Toprol | Toradol |
| Verelan | Verelan |
| Vioxx | Vioxx |



OPDRA will perform name reviews on a first-in, first-out basis or by special timing demands imposed by the Prescription Drug User Fee Act or other regulatory review demands. Before the change in October, the agency evaluated proprietary names at regularly scheduled monthly meetings of LNC. Under the new process, an OPDRA project manager will conduct the name evaluation consultation in a manner similar to that of the NDA review.

The OPDRA project manager will assign a proposed proprietary name to a safety evaluator, who will provide the overall safety risk assessment of the proposed name. Although it is difficult to estimate the time needed for the initial comprehensive review, OPDRA will attempt to complete the risk assessment and issue an opinion to the reviewing division in about 60 calendar days.

The new name review process also involves a change in the number of names accepted for review. Companies should propose only two proprietary names for evaluation, presented in order of preference. If OPDRA finds the first name unacceptable, it will evaluate the second name. If it finds the first name tentatively acceptable, it will not evaluate the second name.

OPDRA will consider only products currently on the market in the United States for potential "sound-alike" and "look-alike" conflicts or other safety risks. Thus, OPDRA will not take into consideration tentatively approved names of other products. In some cases, products available in certain overseas markets may eventually enter the US market, but OPDRA is unable to predict timing for NDA submissions when trademarks become part of the evaluation process.

OPDRA recognizes that most proprietary names presented for review have begun or have completed a registration review at the Patent and Trademark Office (PTO). However, OPDRA cannot base its safety risk assessment only on the issues of confusing similarity that the PTO review addresses. An essential element of the OPDRA risk assessment is the clinical context in which the product will be used. The PTO and FDA reviews serve two fundamentally different purposes.

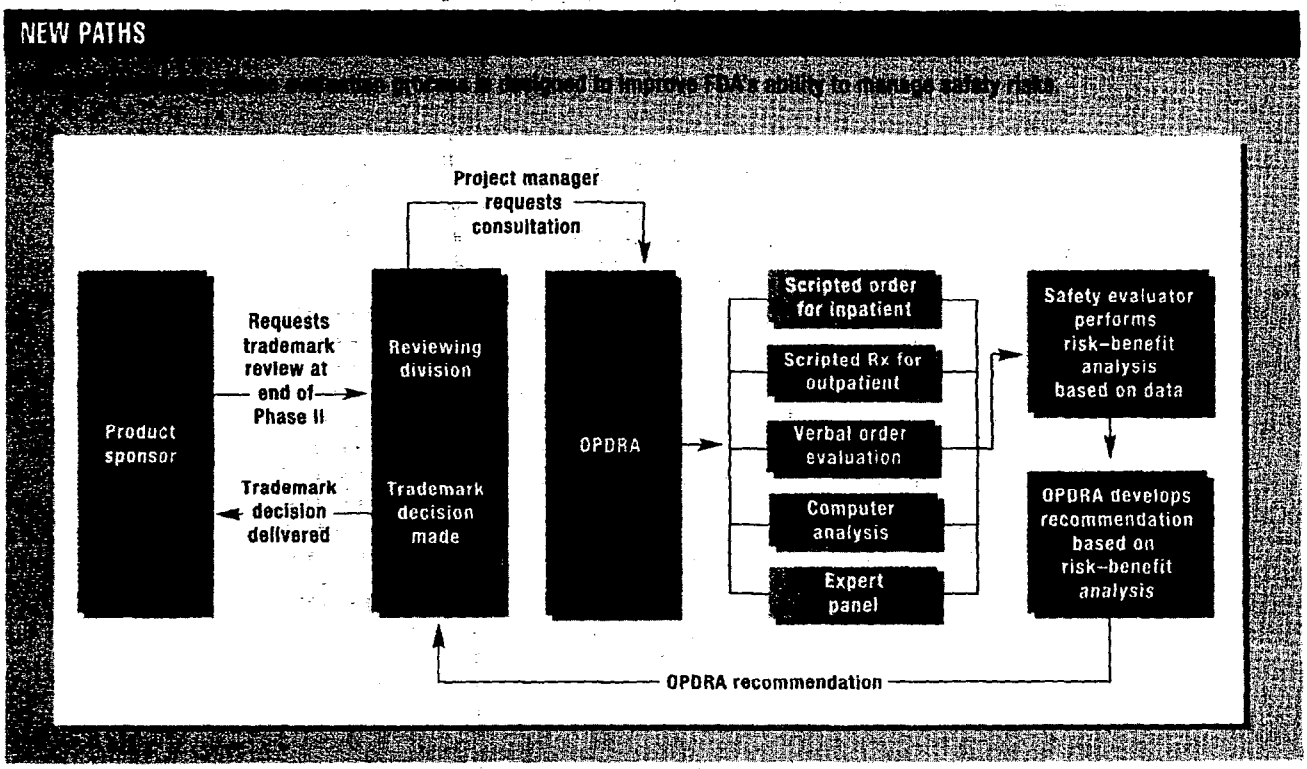
## Technical Analysis

Proprietary names will now undergo a multifactorial review using a uniform systems approach intended to improve consistency and minimize safety risks from medication errors. As indicated, in keeping with the larger OPDRA mission of continuous safety risk assessment, the dominant focus will be on reducing the potential for medication errors associated with look-alike or sound-alike names. FDA recognizes the policy of many companies to have global trademarks, and supports that effort by incorporating many concepts and recommendations set forth by various regulatory and professional organizations.

**Handwriting analysis studies.** Testing will include handwritten test prescriptions for both retail and hospital settings. The analysis includes not only the scripted proprietary name, but also other information such as dose, regimen, and route of administration. About 100 volunteers from various FDA units—including physicians, pharmacists, nurses, and other healthcare professionals—participate in this phase of the evaluation.

**Verbal analysis studies.** This examination involves simulation of clinical settings in

NEW PATHS



which potential errors resulting from sound-alike similarities can be discovered. The process includes recording verbal prescriptions onto a voice recorder for study participant interpretation.

**OPDRA expert group.** Members of OPDRA's medication error staff and a representative from the Division of Drug Marketing, Advertising, and Communication exchange opinions on safety and other nomenclature issues based on professional experiences. They also review criteria for name suitability, such as:

- Does the name imply a clinical promise not supported by the clinical data?
- Does the name suggest an unapproved indication?
- Does the name have an alpha or numerical suffix that could cause confusion?
- Does the name encode a dosage form or regimen?
- Does the name draw too heavily on the generic name?

**Computer-assisted analysis.** OPDRA currently uses FDA computer support for certain elements of proprietary name evaluation, including names on applications undergoing FDA product review. In the future, OPDRA plans to use validated computer software with an associated drug name dictionary to improve FDA's ability to more accurately detect orthographic (spelling) or phonological (sound) similarities in proprietary names.

Once all the data are available, one of six OPDRA evaluators performs a risk–benefit analysis, which forms the basis for the OPDRA recommendation on the acceptability of the proposed trademark. A detailed written recommendation is prepared, then is forwarded to the project manager at the appropriate reviewing division. In some cases, there may be dialogue between OPDRA and the reviewing division prior to acceptance of the OPDRA recommendation. Sponsors are encouraged to contact the project manager at the reviewing division, not OPDRA, for status updates.

FDA continues to upgrade its processes for assessing potential patient risk from prescription drugs. The systems approach to safety risk management, including the creation of a proprietary name evaluation process, has the best promise to date of minimizing medication errors linked to look-alike or sound-alike proprietary names. ■

PROPRIETARY NAMES WILL NOW UNDERGO A MULTIFACTORIAL REVIEW USING A UNIFORM SYSTEMS APPROACH TO IMPROVE CONSISTENCY AND MINIMIZE RISKS FROM MEDICATION ERRORS.

**Ewusi-Mensah, Maame A. F.**

**From:** Hopkins, Jessica R.

**Sent:** Friday, April 11, 2003 11:00 AM

**To:** Ewusi-Mensah, Maame A. F.

**Subject:** FW: Seeking Pharmaceutical Executive article

Maame,

I got a copy from another librarian. They have access to a database that we don't subscribe to. He was able to get the actual image of it though. You'll notice there's a copyright notice at the bottom. I'll let you decide if you want to put white out on it and copy it again if you have to file it or something.

Jessica

## PROOF OF SERVICE BY OVERNIGHT DELIVERY

I declare that I am employed with the law firm of Morrison & Foerster LLP, whose address is 425 Market Street, San Francisco, California, 94105; I am not a party to the within cause; I am over the age of eighteen years and I am readily familiar with Morrison & Foerster's practice for collection and processing of correspondence for overseas delivery and know that in the ordinary course of Morrison & Foerster's business practice the document described below will be deposited in a box or other facility regularly maintained by UPS or delivered to an authorized courier or driver authorized by UPS to receive documents on the same date that it is placed at Morrison & Foerster for collection.

I further declare that on the date hereof I served a copy of:

**Registrant Anticancer, Inc.'s Notice of Reliance: Article from the Journal Pharmaceutical Executive**

on the following by placing a true copy thereof enclosed in a sealed envelope with delivery fees provided for, addressed as follows for collection by UPS at Morrison & Foerster LLP, 425 Market Street, San Francisco, California, 94105, in accordance with Morrison & Foerster's ordinary business practices:

Mark H. Jay, Esq.
Mark H. Jay, P.A.
71 Baltusrol Way
Short Hills, NJ 07078-2457

I declare under penalty of perjury under the laws of the State of California that the above is true and correct.

Executed at San Francisco, California, this 11th day of April, 2003.

Lucia M. Sario

(signature)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | |
|---|---|
| Petitioner: | Alfacell Corporation |
| Registrant: | Anticancer, Inc. |
| Mark: | ONCASE |
| Reg. No.: | 1,987,445 |
| Cancellation No.: | 32,202 |

**CERTIFICATE OF MAILING BY EXPRESS MAIL**

Trademark Trial and Appeal Board
Assistant Commissioner for Trademarks
2900 Crystal Drive
Arlington, VA 22202-3513

Dear Sir:

Express Mail Label No.: EV 240722497 US

Date of Deposit: April 11, 2003

I hereby certify that the attached **Registrant Anticancer, Inc.'s Notice of Reliance: Website of Opposer Alfacell Corp.,; Registrant Anticancer, Inc.'s Notice of Reliance: Printouts from Website of The Center for Drug Evaluation and Research; Registrant Anticancer, Inc.'s Notice of Reliance: Printouts from Website of The Office of Drug Safety; Registrant Anticancer, Inc.'s Notice of Reliance: Article from The Journal Pharmaceutical Executive; Websites Showing The Circulation of Various Scientific Journals** and receipt verification postcard are being deposited with the United States Postal Service Express Mail delivery as "Express Mail Post Office to Addressee" service under 37 C.F.R § 1.10 on the date indicated above, and is addressed to: Trademark Trial and Appeal Board, Assistant Commissioner for Trademarks, 2900 Crystal Drive, Arlington, VA 22202-3513.

Respectfully submitted,

By: _____
Chase Trombella